Exhibit A

Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

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For more on the **IARC Monographs** see http://monographs.iarc.fr

Upcoming meetings

June 2–9, 2015, Volume 113: Some organochlorine insecticides and some chlorphenoxy herbicides

Oct 6–13, 2015, Volume 114: Red meat and processed meat

Monograph Working Group Members

A Blair (USA)—Meeting Chair; L Fritschi (Australia); J McLaughlin; C M Sergi (Canada); G M Calaf (Chile); F Le Curieux (Finland); I Baldi (France); F Forastiere (Italy); H Kromhout (Netherlands); A 't Mannetje (New Zealand); T Rodriguez [unable to attend] (Nicaragua); P Egeghy [unable to attend], G D Jahnke; C W Jameson; M T Martin; M K Ross; I Rusyn; L Zeise (USA)

In March, 2015, 17 experts from 11 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of the organophosphate pesticides tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate (table). These assessments will be published as volume 112 of the IARC Monographs.[1]

The insecticides tetrachlorvinphos and parathion were classified as "possibly carcinogenic to humans" (Group 2B). The evidence from human studies was scarce and considered inadequate. Tetrachlorvinphos induced hepatocellular tumours (benign or malignant) in mice, renal tubule tumours (benign or malignant) in male mice,[2] and spleen haemangioma in male rats. Tetrachlorvinphos is a reactive oxon with affinity for esterases. In experimental animals, tetrachlorvinphos is systemically distributed, metabolised, and eliminated in urine. Although bacterial mutagenesis tests were negative, tetrachlorvinphos induced genotoxicity in some assays (chromosomal damage in rats and in vitro) and increased cell proliferation (hyperplasia in rodents). Tetrachlorvinphos is banned in the European Union. In the USA, it continues to be used on animals, including in pet flea collars.

For parathion, associations with cancers in several tissues were observed in occupational studies, but the evidence in humans remains sparse. In mice, parathion increased bronchioloalveolar adenoma and/or carcinoma in males, and lymphoma in females. In rats, parathion induced adrenal cortical adenoma or carcinoma (combined),[3] malignant pancreatic tumours, and thyroid follicular cell adenoma in males, and mammary gland adenocarcinoma (after subcutaneous injection in females).[4] Parathion is rapidly absorbed and distributed. Parathion metabolism to the bioactive metabolite, paraoxon, is similar across species. Although bacterial mutagenesis tests were negative, parathion induced DNA and chromosomal damage in human cells in vitro. Parathion markedly increased rat mammary gland terminal end bud density.[4] Parathion use has been severely restricted since the 1980s.

The insecticides malathion and diazinon were classified as "probably carcinogenic to humans" (Group 2A). Malathion is used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world. There is limited evidence in humans for the carcinogenicity of malathion. Case-control analyses of occupational exposures reported positive associations with non-Hodgkin lymphoma in the USA,[5] Canada,[6] and Sweden,[7] although no increased risk of non-Hodgkin lymphoma was observed in the large Agricultural Health Study cohort (AHS). Occupational use was associated with an increased risk of prostate cancer in a Canadian case-control study[8] and in the AHS, which reported a significant trend for aggressive cancers after adjustment for other pesticides.[9] In mice, malathion increased hepatocellular adenoma or carcinoma (combined).[10] In rats, it increased thyroid carcinoma in males, hepatocellular adenoma or carcinoma (combined) in females, and mammary gland adenocarcinoma after subcutaneous injection in females.[4] Malathion is rapidly absorbed and distributed. Metabolism to the bioactive metabolite, malaoxon, is similar across species. Malaoxon strongly inhibits esterases; atropine reduced carcinogenesis-related effects in one study.[4] Malathion induced DNA and chromosomal damage in humans, corroborated by studies in animals and in vitro. Bacterial mutagenesis tests were negative. Compelling evidence supported disruption of hormone pathways. Hormonal effects probably mediate rodent thyroid and mammary gland proliferation.

Diazinon has been applied in agriculture and for control of home and garden insects. There was limited evidence for diazinon carcinogenicity

	Activity (current status)	Evidence in humans (cancer sites)	Evidence in animals	Mechanistic evidence	Classification*
Tetrachlorvinphos	Insecticide (restricted in the EU and for most uses in the USA)	Inadequate	Sufficient	..	2B
Parathion	Insecticide (restricted in the USA and EU)	Inadequate	Sufficient	..	2B
Malathion	Insecticide (currently used; high production volume chemical)	Limited (non-Hodgkin lymphoma, prostate)	Sufficient	Genotoxicity, oxidative stress, inflammation, receptor-mediated effects, and cell proliferation or death	2A†
Diazinon	Insecticide (restricted in the USA and EU)	Limited (non-Hodgkin lymphoma, leukaemia, lung)	Limited	Genotoxicity and oxidative stress	2A†
Glyphosate	Herbicide (currently used; highest global production volume herbicide)	Limited (non-Hodgkin lymphoma)	Sufficient	Genotoxicity and oxidative stress	2A†

EU=European Union. *See the International Agency for Research on Cancer (IARC) preamble for explanation of classification system (amended January, 2006). †The 2A classification of diazinon was based on limited evidence of carcinogenicity in humans and experimental animals, and strong mechanistic evidence; for malathion and glyphosate, the mechanistic evidence provided independent support of the 2A classification based on evidence of carcinogenicity in humans and experimental animals.

Table: **IARC classification of some organophosphate pesticides**

in humans. Positive associations for non-Hodgkin lymphoma, with indications of exposure–response trends, were reported by two large multicentre case-control studies of occupational exposures.[5,6] The AHS reported positive associations with specific subtypes, which persisted after adjustment for other pesticides, but no overall increased risk of non-Hodgkin lymphoma.[11] Support for an increased risk of leukaemia in the AHS was strengthened by a monotonic increase in risk with cumulative diazinon exposure after adjustment for other pesticides. Multiple updates from the AHS consistently showed an increased risk of lung cancer with an exposure–response association that was not explained by confounding by other pesticides, smoking, or other established lung cancer risk factors.[12] Nonetheless, this finding was not replicated in other populations. In rodents, diazinon increased hepatocellular carcinoma in mice and leukaemia or lymphoma (combined) in rats, but only in males receiving the low dose in each study. Diazinon induced DNA or chromosomal damage in rodents and in human and mammalian cells in vitro. Some additional support for human relevance was provided by a positive study of a small number of volunteers exposed to a diazinon formulation.[13]

Glyphosate is a broad-spectrum herbicide, currently with the highest production volumes of all herbicides. It is used in more than 750 different products for agriculture, forestry, urban, and home applications. Its use has increased sharply with the development of genetically modified glyphosate-resistant crop varieties. Glyphosate has been detected in air during spraying, in water, and in food. There was limited evidence in humans for the carcinogenicity of glyphosate. Case-control studies of occupational exposure in the USA,[14] Canada,[6] and Sweden[7] reported increased risks for non-Hodgkin lymphoma that persisted after adjustment for other pesticides. The AHS cohort did not show a significantly increased risk of non-Hodgkin lymphoma. In male CD-1 mice, glyphosate induced a positive trend in the incidence of a rare tumour, renal tubule carcinoma. A second study reported a positive trend for haemangiosarcoma in male mice.[15] Glyphosate increased pancreatic islet-cell adenoma in male rats in two studies. A glyphosate formulation promoted skin tumours in an initiation-promotion study in mice.

Glyphosate has been detected in the blood and urine of agricultural workers, indicating absorption. Soil microbes degrade glyphosate to aminomethylphosphoric acid (AMPA). Blood AMPA detection after poisonings suggests intestinal microbial metabolism in humans. Glyphosate and glyphosate formulations induced DNA and chromosomal damage in mammals, and in human and animal cells in vitro. One study reported increases in blood markers of chromosomal damage (micronuclei) in residents of several communities after spraying of glyphosate formulations.[16] Bacterial mutagenesis tests were negative. Glyphosate, glyphosate formulations, and AMPA induced oxidative stress in rodents and in vitro. The Working Group classified glyphosate as "probably carcinogenic to humans" (Group 2A).

We declare no competing interests.

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Exhibit B

International Agency for Research on Cancer

World Health Organization

20 March 2015

IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides

Lyon, France, 20 March 2015 – The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization, has assessed the carcinogenicity of **five organophosphate pesticides**. A summary of the final evaluations together with a short rationale have now been published online in The Lancet Oncology, and the detailed assessments will be published as Volume 112 of the IARC Monographs.

What were the results of the IARC evaluations?

The herbicide **glyphosate** and the insecticides **malathion** and **diazinon** were classified as *probably carcinogenic to humans* (Group 2A).

The insecticides **tetrachlorvinphos** and **parathion** were classified as *possibly carcinogenic to humans* (Group 2B).

What was the scientific basis of the IARC evaluations?

The pesticides **tetrachlorvinphos** and **parathion** were classified as *possibly carcinogenic to humans* (Group 2B) based on convincing evidence that these agents cause cancer in laboratory animals.

For the insecticide **malathion**, there is *limited evidence of carcinogenicity* in humans for non-Hodgkin lymphoma and prostate cancer. The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. Malathion also caused tumours in rodent studies. Malathion caused DNA and chromosomal damage and also disrupted hormone pathways.

For the insecticide **diazinon**, there was *limited evidence of carcinogenicity* in humans for non-Hodgkin lymphoma and lung cancer. The evidence in humans is from studies of agricultural exposures in the USA and Canada published since 2001. The classification of diazinon in Group 2A was also based on strong evidence that diazinon induced DNA or chromosomal damage.

For the herbicide **glyphosate**, there was *limited evidence of carcinogenicity* in humans for non-Hodgkin lymphoma. The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. In addition, there is convincing evidence that glyphosate also can cause cancer in laboratory animals. On the basis of tumours in mice, the United States Environmental Protection Agency (US EPA) originally classified glyphosate as *possibly carcinogenic to humans* (Group C) in 1985. After a re-evaluation of that mouse study, the US EPA changed its classification to *evidence of non-carcinogenicity in humans* (Group E) in 1991. The US EPA Scientific Advisory Panel noted that the re-evaluated glyphosate results were still significant using two statistical tests recommended in the IARC Preamble. The IARC Working Group that conducted the evaluation considered the significant findings from the US EPA report and several more recent positive results in concluding that there is *sufficient evidence of carcinogenicity* in experimental animals. Glyphosate also caused DNA and chromosomal damage in human cells, although it gave negative results in tests using bacteria. One study in community residents reported increases in blood markers of chromosomal damage (micronuclei) after glyphosate formulations were sprayed nearby.

How are people exposed to these pesticides?

Tetrachlorvinphos is banned in the European Union. In the USA, it continues to be used on livestock and companion animals, including in pet flea collars. No information was available on use in other countries.

Parathion use has been severely restricted since the 1980s. All authorized uses were cancelled in the European Union and the USA by 2003.

IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides

Malathion is currently used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world. Workers may be exposed during the use and production of malathion. Exposure to the general population is low and occurs primarily through residence near sprayed areas, home use, and diet.

Diazinon has been applied in agriculture and for control of home and garden insects. Production volumes have been relatively low and decreased further after 2006 due to restrictions in the USA and the European Union. Only limited information was available on the use of these pesticides in other countries.

Glyphosate currently has the highest global production volume of all herbicides. The largest use worldwide is in agriculture. The agricultural use of glyphosate has increased sharply since the development of crops that have been genetically modified to make them resistant to glyphosate. Glyphosate is also used in forestry, urban, and home applications. Glyphosate has been detected in the air during spraying, in water, and in food. The general population is exposed primarily through residence near sprayed areas, home use, and diet, and the level that has been observed is generally low.

What do Groups 2A and 2B mean?

Group 2A means that the agent is ***probably*** *carcinogenic to humans*. This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. *Limited evidence* means that a positive association has been observed between exposure to the agent and cancer but that other explanations for the observations (called chance, bias, or confounding) could not be ruled out. This category is also used when there is limited evidence of carcinogenicity in humans and strong data on how the agent causes cancer.

Group 2B means that the agent is ***possibly*** *carcinogenic to humans*. A categorization in Group 2B often means that there is convincing evidence that the agent causes cancer in experimental animals but little or no information about whether it causes cancer in humans.

Why did IARC evaluate these pesticides?

The IARC Monographs Programme has evaluated numerous pesticides, some as recently as 2012 (anthraquinone, arsenic and arsenic compounds). However, substantial new data are available on many pesticides that have widespread exposures. In 2014, an international Advisory Group of senior scientists and government officials recommended dozens of pesticides for evaluation. Consistent with the advice of the Advisory Group, the recent IARC meeting provided new or updated evaluations on five organophosphate pesticides.

How were the evaluations conducted?

The established procedure for Monographs evaluations is described in the Programme's Preamble. Evaluations are performed by panels of international experts, selected on the basis of their expertise and the absence of real or apparent conflicts of interest. For Volume 112, a Working Group of 17 experts from 11 countries met at IARC on 3–10 March 2015 to assess the carcinogenicity of **tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate**. The in-person meeting followed nearly a year of review and preparation by the IARC secretariat and the Working Group, including a comprehensive review of the latest available scientific evidence. According to published procedures, the Working Group considered "reports that have been published or accepted for publication in the openly available scientific literature" as well as "data from governmental reports that are publicly available". The Working Group did not consider summary tables in online supplements to published articles, which did not provide enough detail for independent assessment.

What are the implications of the IARC evaluations?

The Monographs Programme provides scientific evaluations based on a comprehensive review of the scientific literature, but it remains the responsibility of individual governments and other international organizations to recommend regulations, legislation, or public health intervention.

Media inquiries: please write to com@iarc.fr. Thank you.

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Exhibit C

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: March 31, 2015

Subject: Response to Public Comments Received Regarding EPA Endangered Species Assessment for 2,4-D Choline Salt in Arkansas, Kansas, Louisiana, Minnesota, Missouri, Mississippi, Nebraska, Oklahoma, Tennessee, and North Dakota[a]

Product Name: Enlist Duo™

EPA Registration Number: 62719-649

Application Date: November 1, 2011

On October 16, 2014 the Environmental Protection Agency (EPA) published for comment an Endangered Species Assessment regarding the proposed use of Enlist Duo in the following 10 states: Arkansas, Kansas, Louisiana, Minnesota, Missouri, Mississippi, Nebraska, Oklahoma, Tennessee, and North Dakota. However, EPA is not going forward at this time with registering Enlist Duo for use in Tennessee.

The initial Enlist Duo registration allowed use in 6 states: Illinois, Indiana, Iowa, Ohio, South Dakota, and Wisconsin. The only proposed change to the Enlist Duo registration under consideration on October 16, 2014 was the addition of the 10 new states, and the only new evaluation done by EPA concerning this change was the Endangered Species Assessment published for comment on October 16, 2014. EPA did not solicit comments outside the scope of the Endangered Species Assessment for the 10 new states. EPA previously considered comments on the original Enlist Duo registration and addressed them in the original registration decision and response to comments document. The original registration decision, response to comments document, and all of the materials supporting the original registration are available in Docket ID: EPA-HQ-OPP-2014-0195, as is the Endangered Species Assessment regarding the addition of the 10 new states. Comments received during this public participation process not

[a] Although EPA published for comment, on October 15, 2014, an Endangered Species Assessment regarding the proposed use of Enlist Duo in the 10 states of Arkansas, Kansas, Louisiana, Minnesota, Missouri, Mississippi, Nebraska, Oklahoma, Tennessee, and North Dakota, EPA is not going forward at this time with registering Enlist Duo for use in Tennessee.

related to the Endangered Species Assessment pertaining to the 10 new states are not discussed in this response.

The Agency received 34,526 comments in response to this public participation process. The EPA welcomes input from the public during the decision process when amending pesticide registrations, and is committed to thoroughly evaluating and mitigating any potential risks from registered pesticides, consistent with applicable statutory standards. Also, EPA strives to document and explain the basis of its regulatory decisions through public documents.

The majority of the comments received were outside the scope of this action – the Endangered Species Assessment for the 10 (now 9) additional states. EPA notes that its previous response to comments addressed virtually all of these concerns. Commenters are referred to Docket ID: EPA-HQ-OPP-2014-0195 for those responses and any additional information regarding the decision to register Enlist Duo.

Relevant comments concerning the Endangered Species Assessment that were raised for the additional states are discussed below

1. *"No effect" determinations are arbitrary and capricious because they follow the old system. (i.e., species within the action area were found to be not affected if there were no indirect or direct effects pertinent to the species) and did not follow the National Academy of Sciences report recommendations regarding pesticide mixtures; sublethal, indirect, and cumulative effects; and surrogate species.*

   As stated in a recent report to Congress submitted by EPA, the National Marine Fisheries Service (NMFS), the U.S. Fish and Wildlife Service (USFWS), and the U.S. Department of Agriculture (USDA):

   > "EPA scientists used highly conservative and protective assumptions to evaluate ecological risks for the new uses of 2,4-D in Enlist Duo. The assessments confirm that these uses meet safety standards for pesticide registration, and as approved, will be protective of non-target species, including endangered species."

   Interim Report to Congress on Endangered Species Act Implementation in Pesticide Evaluation Programs ("Interim Report") at 20 (Dec. 11, 2014), *available at* http://www.epa.gov/oppfead1/endanger/2014/esa-reporttocongress.pdf. Additionally, the Interim Report shows that the combined agencies acknowledge that EPA's evaluation of 2,4-D in Enlist Duo was appropriately based on EPA's "Overview Document-compliant endangered species assessment for new herbicide tolerant crop uses" (*Id.* at 22), referring to EPA's Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, U.S. Environmental Protection Agency – Endangered and Threatened Species Effects Determinations ("Overview Document") (January 23, 2004), *available at* http://www.epa.gov/oppfead1/endanger/consultation/ecorisk-overview.pdf.

2. *EPA's determinations that listed species are not expected to occur in an action area is arbitrary and capricious. EPA may not limit the scope of the action area to the treated field, EPA must consult if it is known that the chemical will move off the field.*

EPA relied on U.S. Fish and Wildlife and National Marine Fisheries Services (the Services) location information, habitat information, and the results of the screening assessment (with risk mitigation measures in place) to establish the relationship of species locations with the expected area where the pesticide exposure would rise to the point where effects were reasonably expected to take place for **any** taxonomic group. The Agency makes no claim that drift and runoff do not occur. The Agency characterized the levels of exposure to drift and runoff and determined that, with mitigations in place, exposures high enough to cause acute or chronic effects are not reasonably expected to occur in aquatic systems adjacent to treated fields, nor to any place suitable for wildlife adjacent to fields for any taxonomic group. The Agency clearly stated in the screening assessment that exposures were only above levels of concern to organisms on treated fields.

EPA used the available terrestrial and aquatic listed species locations by state and the available habitat requirement information from the Services to compare with the locations of treated use sites. If a species did not occur in a county where the use sites occur, the species was reasonably expected to have no effects because it was not co-located with the use site. If a species was in a county where the use site was located, it was assumed that it was possible it could be co-located with the action areas (the area where effects occur is defined by the geographical extent where exposure would elicit effects to any taxonomic group) and that further evaluation was necessary to determine if this was actually the case. In such situations the Agency consulted biological information from the Services to determine if the species occurred within the action area.

If according to the Services, a listed species was an aquatic species without a terrestrial phase, it was expected to occupy an aquatic environment, and the screening-level risk assessment found no exposures sufficient to elicit effects in aquatic environments. Consequently, the Agency concluded aquatic species are not in the action area.

If a listed species was a terrestrial organism in any phase according to the Services, it was assumed to occupy habitats that were not otherwise managed to the exclusion of listed species (i.e. areas not paved, not enclosed by structures, or areas in row crop). Since the steps above found that mitigations prevented pesticide exposure to rise to levels reasonably expected to cause effects in areas other than the treated use site, no effects would occur to these off-field organisms. Exposure could still occur, just not at levels that would trigger any effects concerns for any taxonomic group. For species for which USFWS information suggested occurrence on a use site at any time during their life cycle, the Agency turned to the biology of the species to determine whether species-specific information would refine the screening-level risk conclusions. If the effects expected on the field were not directly related to direct effects to the listed species, did not affect any resource the species needed, nor upon reassessment of the risk calculations show a species-specific finding that exposures rose to a level of concern, the Agency concluded "no effect."

3. *Exposure to the pesticide alone is enough to conclude a "may affect." Reliance on RQ values to make this determination is inappropriate.* As noted above in response to Comment #1, a recent report to Congress submitted by EPA, NMFS, USFWS, and USA stated:

> "EPA scientists used highly conservative and protective assumptions to evaluate ecological risks for the new uses of 2,4-D in Enlist Duo. The assessments confirm that these uses meet safety standards for pesticide registration, and as approved, will be protective of non-target species, including endangered species."

Interim Report at 20 (Dec. 11, 2014). Additionally, the Interim Report shows that the combined agencies acknowledge that EPA's evaluation of 2,4-D in Enlist Duo was appropriately based on EPA's "Overview Document-compliant endangered species assessment for new herbicide tolerant crop uses" (*Id*. at 22), referring to EPA's Jan. 23, 2004 "Overview Document" regarding endangered and threatened species effects.

4. The Agency did not use or review ECOTOX data.

The Agency relied on previously evaluated data sets from earlier 2,4-D risk assessments, which included ECOTOX data.

5. The Agency failed to allow for uncertainty in the analysis of effects to honeybees and the non-definitive endpoints for other taxa.

The honeybee data and other non-definitive data were used as surrogate toxicology information for non-target species, including listed species. Non-definitive data were "greater than" values, meaning that the highest toxicity level tested did not result in an acute endpoint (i.e., the LD_{50} is greater than the highest concentration of 2,4-D that was tested). The Agency relied on the best available data within the confines of data sets from previous 2,4-D risk assessments. Exposure estimates were compared to the available data and showed exposure levels below what was reasonably and conservatively expected to be effects endpoints.

6. The Agency did not account for the combined effects of glyphosate and 2,4-D.

The Agency looked at available 2,4-D/glyphosate combined data from the scientific peer-reviewed literature and registrant-submitted information for mammal, freshwater invertebrates and freshwater fish and found no combined effects that exceeded the expected effects of glyphosate or 2,4-D individually.

7. EPA failed to consider glyphosate effects.

Since the registration of Enlist Duo does not contain any new use for glyphosate, as it has been registered for use on genetically engineered corn and soybeans for several years now and is presently used on the majority of those crops' production acres, EPA did not conduct a new assessment for the glyphosate portion of Enlist Duo. Also, EPA's decision did not

authorize any change in when, where, how, or how much glyphosate can be used from what is already authorized under FIFRA.

8. *Indiana bat. EPA arbitrarily used assumptions of farm field foraging frequency to reduce exposure levels below the concern threshold. EPA, by admitting that 2,4-D exposure would occur, is bound to make a "may affect" determination.*

EPA undertakes a careful and extensive scientific analysis in all of its ESA-related pesticide effects analyses, as it did here. The Agency begins its screening level assessments by conducting a basic ecological risk assessment. That assessment uses broad default assumptions to establish estimated environmental concentrations of particular pesticides. If that screening level assessment results in a determination that the pesticide has no effect on listed species, EPA preserves its limited resources by stopping there. On the other hand, where the screening level assessment does not result in a no effect finding, EPA then uses increasingly specific methods and exposure models to refine its estimated environmental concentrations. At each screening step, EPA compares the more refined concentrations to the toxicity of the pesticide active ingredient to determine whether the pesticide exceeds levels of concern established for listed aquatic and terrestrial species. EPA determines that there is "no effect" on listed species if, at any step in the screening level assessment, no levels of concern are exceeded. If, after performing all the steps in the screening level assessment, a pesticide still exceeds the Agency's levels of concern for listed species, EPA then conducts a species-specific assessment to make effects determinations for individual listed species. That assessment, unlike the screening level assessment, takes account of species' habitats and behaviors to determine whether any listed species may be affected by use of the pesticide.

EPA followed this careful and methodical tiered approach here. In 2013, EPA performed a screening level risk assessment of the proposed new uses of 2,4-D in Enlist Duo. The Agency subsequently refined its endangered species risk assessment based on spray drift mitigation language that Dow AgroSciences added to the Enlist Duo label at EPA's request. Specifically, EPA noted that the spray drift language would limit drift by requiring end users to utilize a particular nozzle and mix formulation. This language also required end-users to employ a substantial buffer when the wind is blowing toward any area that is not a field in crop cultivation, paved area, or area covered by buildings and other structures.

EPA next took into account species-specific biological information as it relates to the timing of Enlist Duo applications (and thus potential exposure to 2,4-D). EPA's refined analysis observed that Indiana bats typically forage in closed to semi-open forested habitats and forest edges and prefer to forage in wooded areas. A ranking of the foraging use of habitats suggested the following order of foraging preference: (a) roads; (b) forests; (c) riparian areas; (d) grasslands; (e) agricultural areas. EPA's refined analysis went on to analyze the likelihood that the bat could use agricultural land as a source of prey. EPA concluded that the bat could make use of agricultural land as a source of prey and roost in patches of fragmented forest that are adjacent to corn and soybean fields. The extent of foraging over agricultural land, however, would be less than the degree of foraging around the canopies of forested areas.

EPA conservatively estimated that 33% of the bat's diet could be consumed over agricultural lands. EPA incorporated this and other data, such as the metabolized energy in bat prey, the daily food ingestion rate scaled to individual bat bodyweight, and the agricultural application rate of 2,4-D. Taken together, EPA's analysis established a complete exposure pathway for Indiana bats to 2,4-D for those times when the bat does forage over treated fields. EPA concluded that no bat would experience even one day of exposure exceeding the applicable toxicological threshold. Accordingly, EPA determined that the 2,4-D component of Enlist Duo would have no effect on the Indiana bat.

Again, as noted above in response to comment #1 and #3, a recent report to Congress submitted by EPA, NMFS, USFWS, and USA stated:

> "EPA scientists used highly conservative and protective assumptions to evaluate ecological risks for the new uses of 2,4-D in Enlist Duo. The assessments confirm that these uses meet safety standards for pesticide registration, and as approved, will be protective of non-target species, including endangered species."

Interim Report at 20 (Dec. 11, 2014). Additionally, the Interim Report shows that the combined agencies acknowledge that EPA's evaluation of 2,4-D in Enlist Duo was appropriately based on EPA's "Overview Document-compliant endangered species assessment for new herbicide tolerant crop uses" (*Id*. at 22), referring to EPA's Jan. 23, 2004 "Overview Document" regarding endangered and threatened species effects.

9. *Louisiana Black Bear. Despite the screening-level assessment trigger for concerns, the Agency made up additional components to its illogical assessment to reach a "no effect." These kind of specific biological assumptions are outside of EPA's expertise and are suspect.*

Once the screening level assessment and co-location analysis suggested the bear was potentially at risk, the Agency compared available biological/behavioral data identified in the literature and in USFWS sources to determine if the exposure assumptions employed in the conservative screening assessment were biologically appropriate for the bear. Based on this review, more relevant exposure inputs were developed for the bear (i.e., seasonal timing of when the bear is expected to use agricultural fields) and the risk assessment was refined to reflect these additional lines of evidence. The refined analysis indicated that the exposures were overestimated in the screen, and exposures under more biologically relevant conditions were below levels of concern.

10. *Whooping Crane. EPA did not reproduce the calculations for this 10-state assessment that was done for the previous six states. EPA did not conduct a chronic assessment nor consider residues on all the food items consumed by the crane.*

The chronic assessment for all bird species (including the whooping crane) was included in the screening risk assessment and found no risk concerns for birds; only concerns for acute effects were identified. The assumptions at the screening-level are intentionally more

conservative than species-specific analyses; thus, the lack of chronic concerns at the screening-level indicated that further refinement would not identify risk and was not necessary. EPA did not repeat all the calculations in the 10-state assessment because the findings in the previous assessment were based on identical assumptions of exposure and toxicity regardless of the state in which the species occurs. Consequently, citing the documents in which these analyses were contained was appropriate.

The dietary analysis was performed on the food item that contained the highest 2,4-D residues. By assuming that 100 percent of the diet was made up of the food item with the highest residues, the analysis is protective of food items with lower residues as well.

11. *Mississippi Sandhill Crane. The assessment ignored chronic effects nor did it consider residues on all of the food items in the crane's diet. The RQ fell just below the level of concern, so EPA should check its fuzzy math. Given the sensitive status of the crane (located on and adjacent to the Mississippi Sandhill Crane National Wildlife Refuge), Enlist Duo should not be registered in Mississippi.*

See Comment 10 for a response to the chronic effects and dietary analyses. The Agency applied the level of concern analysis in an objective manner. The resulting exposure-to-effects ratio is below the concern level that the Agency has used under the evaluation approach selected for this assessment. Consequently, "no effects" are expected for the Mississippi Sandhill Crane.

12. *Lesser Prairie Chicken. The Agency failed to conduct a chronic effects assessment. EPA's attempts to pretend to understand lesser prairie chicken biology by citing a few random scientific journal articles is laughable, absurd, and otherwise arbitrary and capricious.*

See Comment 10 for a response to the chronic effects analysis. EPA relied on publically available published information that described the extent to which the lesser prairie chicken uses agricultural environments. These findings were compared to the assumptions made in the screening assessments and all lines of evidence lead to a conclusion that the species would not be exposed to 2,4-D choline salt at the levels that were assumed in the screen. This initiated a more biologically-relevant exposure estimate that resulted in a finding that exposures fell below the concern level for this species. EPA did not find any data showing agricultural field use by the species from USFWS reports and citations made in those reports or reports citing those references.

13. *Gopher Tortoise. The Agency did not complete a chronic assessment. Exposure demonstrates that the species is affected.*

Birds are used as surrogates for reptiles under the assessment approach when data are unavailable for reptiles (USEPA 2004). Birds are likely a conservative surrogate for exposure to pesticide residues via the diet due to their higher metabolic rate as warm-blooded creatures compared to cold-blooded reptiles, which suggests that food consumption rates, and

therefore dietary pesticide consumption rates, would be higher for birds. Furthermore, with respect to chronic assessment and its reproductive endpoints, both birds and the majority of reptiles are egg-layers representing very similar exposure scenarios en-ovo. The screening assessment found no chronic concerns for birds and thus no chronic concerns for reptiles.

14. *American Burying Beetle. There are no established levels of concern for terrestrial invertebrates, presumably because EPA seeks to register pesticides that kill terrestrial invertebrates. EPA cites DP411614 as reason for "no effect" and it is not in the record. EPA did not consider direct effects (i.e., brushing up against treated plants) to the beetle.*

The Agency has established an interim level of concern of 0.05 that has been used for litigation assessments and other endangered species risk assessments. Direct effects to terrestrial invertebrates (e.g., the American burying beetle) were assessed in the screening-level risk assessment and EPA concluded that direct effects were not a concern. Therefore, only indirect effects to the American burying beetle were considered in the refined endangered species analysis because direct effects had already been screened out (see whooping crane response for more discussion on screening assessments). EPA did not repeat the analysis for the American burying beetle in the 10-state assessment because the findings in the previous assessment (6-state endangered species assessment, DP411614) were based on identical assumptions of exposure and toxicity regardless of the state in which the species occurs. Consequently, citing the DP barcode of the document in which this analysis was contained was appropriate. DP411614 was placed in the docket in April 2014 (EPA-HQ-OPP-2014-0195-005).

15. *Spring Creek Bladderpod. By EPA's own tortured logic, the pesticide cannot be approved for use in Wilson County, TN. Enlist Duo should not be registered in Tennessee.*

EPA is not going forward at this time with registering Enlist Duo for use in Tennessee.

16. *EPA did not consider populations of its eleven identified listed species that are being reintroduced or expanding ranges into areas of the states where corn and soybean are grown.*

In reaching effects determinations, the Agency referred to species recovery plans, species 5-year reviews, and United States Fish and Wildlife Service (USFWS) county-level summaries of occurrence. A species was considered if USFWS information indicated endangered or threatened populations were located within any of the states included in this assessment.

17. *The Agency failed to assess adverse modification or destruction of critical habitat.*

Effects for any biologically mediated process are likely limited to the area where exposure to the herbicide rises to the level of affecting one or more taxonomic groups. The Agency demonstrated that effects are limited to the agricultural field, and possibly paved areas and areas enclosed by structures. Consequently, critical habitat effects for any species would be limited to the areas where biological effects on a single individual could be reasonably

expected to occur (i.e., treated fields, paved areas, and areas enclosed by structures). A detailed analysis is provided in the addendum to the 2,4-D choline salt assessment on corn and soybean – critical habitat analysis (USEPA 2015, D425283, Docket ID: EPA-HQ-OPP-2014-0195-3688).

18. *EPA's assumption that spray drift will remain confined to the field because of the spray drift mitigation language is flawed. Similarly, EPA claims that there will be no 2,4-D choline salt in surface waters and that "the proposed 2,4-D choline uses are not expected to overlap with rivers, streams, creeks, or other water bodies."*

The Agency makes no claim that spray drift or runoff will not occur; rather it states that with mitigations in place, exposures high enough to cause acute or chronic effects are not reasonably expected to occur in aquatic systems adjacent to treated fields, nor to any place suitable for wildlife adjacent to fields for any taxonomic group. The Agency based the spray drift mitigation on empirical field data with Enlist Duo as well as the consideration of habitats for non-target organisms. Given that 2,4-D choline salt use is restricted to corn and soybean fields that are in agricultural production, no water bodies are expected to be within the action area (*i.e.*, the field). Consequently, this is a reasonable rationale for the "no effects" determinations for aquatic species.

19. *Non-target species may move on and off the field during spraying. The Agency has not indicated how the 168 endangered plant and animals in its 2,4-D assessment would be informed of these field boundaries so as to remain off of the field.*

The Agency's endangered species analysis considered whether a species would be on the field at any time, based on species-specific biology and habits, taken from USFWS' and National Marine Fisheries Service's documents. Consequently, those species that may move on and off the field were captured in this analysis and considered as being "on" the field.

20. *Effects of the whole product, Enlist Duo (including active ingredients and the additional unidentified ingredients) have not been assessed. In addition, synergistic or additive effects of Enlist Duo with atrazine or other commonly used herbicides have not been assessed. Risk to terrestrial plants and other organisms have been underestimated because formulation data are not available. Indirect effects, such as loss of critical food, forage and nesting sites resulting from reduced plant diversity associated with increased spraying of the whole product, Enlist Duo (separately and in combination with other pesticide products) has not been assessed.*

The response to public comments for the initial registration of Enlist Duo on corn and soybeans includes a more detailed analysis on the potential for synergy between the 2,4-D choline salt and glyphosate (Document ID number EPA-HQ-OPP-2014-0195-2414). In summary, if effects data are available for a formulated product containing more than one active ingredient, they may be used qualitatively or quantitatively in accordance with the Agency's Overview Document and the Services' Evaluation Memorandum (USEPA 2004;

USFWS/NMFS/NOAA 2004). Acute oral rat data were available for the Enlist Duo product as formulated and did not indicate any additive or synergistic effects when compared with 2,4-D by itself. Because the available data showed no indication that the tested results would be different for untested species, this conclusion was extended to all animal taxa. For animal taxa where Enlist Duo formulation data were not available, the most sensitive 2,4-D acid/salt/amine endpoint was used, as a protective surrogate. For terrestrial plants, formulation data were available for a number of other 2,4-D products; the most sensitive of these was selected to represent the toxicity of Enlist Duo. The Agency does not routinely assess tank mixes, consequently, Enlist Duo tank-mixed with atrazine or other commonly used herbicides was not assessed.

The spray drift mitigation language on the label is expected to keep exposure levels below the threshold of concern to <u>any</u> species off of the field. Consequently, only indirect effects that take place on a treated corn or soybean field needed to be considered. This was included in the endangered species risk assessment.

21. *The Agency did not follow its own guidance document for honeybee toxicity assessment and thereby underestimates the risks to bees and other beneficial insects. Specifically, indirect (e.g., effect of reduced flowering plants for foraging) and direct exposures, the differential sensitivity of larvae compared to adult bees, sub-lethal effects that may affect brood and colony health, and differences in sensitivity when exposed via that contact or oral route were not considered. These data gaps should be filled before approving the registration of Enlist Duo. EPA inappropriately classifies 2,4-D as "practically non-toxic" to honeybees and fails to consider sub-lethal effects, and the importance of these on hive health and colony collapse disorder. 2,4-D could also affect other important insect species such as monarch butterflies. Glyphosate was not included in the assessment.*

The response to public comments for the initial registration of Enlist Duo on corn and soybeans includes a honeybee analysis in accord with the Agency's Pollinator Risk Assessment Framework and includes adult acute oral and contact data (ID# EPA-HQ-OPP-2014-0195-2414). The analysis indicated that risk concerns are not expected for acute exposures to adult honeybees. Sub-lethal signs of toxicity in the contact study included lethargy and loss of equilibrium in a total of three bees at the highest treatment level. The loss of equilibrium was only observed at the 24 hour observation period and the lethargy was only observed at 72 hours. For the acute oral study, reduced coordination was the only sub-lethal effect noted in the three highest treatments at 4 hours (2, 1, and 5 bees at 23.2, 42.0 and 62.6 µg ae/bee treatment levels). At the 24 hour and 48 hour observation periods, only 1 bee was affected in each of the two highest treatment groups. Overall, the sub-lethal effects appear limited and it is unlikely that they would translate into whole colony effects given their limited magnitude.

Agency policy is that any pesticide with an acute LD_{50} > 11 µg ae/bee is considered "practically non-toxic" to honeybees, based on mortality. Generic data gaps for larval

honeybees and chronic exposures to adults are being considered as part of the ongoing Registration Review process.

The endangered species assessment considered both direct and indirect risk concerns (for example, risk concerns for flowering plants) in its analysis, including those to honeybees, monarch butterflies, and other terrestrial invertebrates.

Since the registration of Enlist Duo does not contain any new use for glyphosate, as it has been registered for use on genetically engineered corn and soybeans for several years now and is presently used on the majority of those crops' production acres, EPA did not conduct a new assessment for the glyphosate portion of Enlist Duo. Also, EPA's decision did not authorize any change in when, where, how, or how much glyphosate can be used from what is already authorized under FIFRA.

22. *Large-scale spraying of 2,4-D would contaminate and poison plants and animals in the vicinity of the sprayed fields, leading to economical and environmental damage. The spray drift assessment is impaired by EPA's reliance on models rather than real-world data.*

The Enlist Duo label approved by EPA contains enforceable spray drift mitigation requirements that will prevent 2,4-D choline salt from moving off the field in concentrations high enough to exceed our levels of concern in non-target species, including listed species. EPA uses the best available data and models in its spray drift assessments. The mitigation requirements are based on Enlist Duo specific field and laboratory data; the spray drift analyses were tailored specifically to the Enlist Duo use patterns, environmental conditions, and formulation data. If additional data become available, EPA will consider it for incorporation into future analyses, as appropriate.

23. *There are multiple gaps in the 2,4-D volatilization and spray drift data that were submitted to the Agency. The data that do exist indicate that there may be risks for terrestrial plants and for endangered species of mammals and birds from 2,4-D drift off the treated fields.*

See the response to public comments for the initial registration of Enlist Duo (ID# EPA-HQ-OPP-2014-0195-2414) for a robust discussion of the spray drift and volatilization data available for the 2,4-D choline salt and the lines of evidence used to arrive at conclusions. The screening-level assessment was designed to be very conservative and flagged potential risk concerns for terrestrial plants, mammals, and birds. Upon refinement of the assessment using species specific information (i.e., body weight, species location, timing of species' use of agricultural fields), it was concluded that "no effects" are anticipated for endangered species in the 8 states in which the Agency is registering Enlist Duo for use at this time.

24. *EPA did not consider the effects of increased use in 2,4-D that will occur if Enlist Duo is registered on corn and soybean in AR, KS, LA, MN, MO, MS, NE, ND, OK, and TN.*

The ecological risk assessment and endangered species risk assessment assume an organism is exposed to the maximum amount of 2,4-D choline salt that is possible (terrestrial and aquatic exposure pathways), given that the label directions are followed. Consequently, the risk assessment is protective and does not need to be adjusted for the actual number of acres that are treated with Enlist Duo.

25. Risks associated with runoff of Enlist Duo are not adequately assessed by EPA.

On October 10, 2014, the Agency issued an addendum that characterized the amount of runoff that would be expected from the proposed 2,4-D choline salt uses. Using PRZM/EXAMS, it was determined that the amount of runoff expected from the corn and soybean uses is <1% of the applied mass. This is well below the assumptions made by the TerrPlant model, which was used as a Tier 1 screening-model for risk concerns. Through this analysis EPA found that concentrations of 2,4-D choline in runoff will not present a concern to terrestrial plants. See USEPA 2014 (D423309) for more details of the analysis.

26. Metabolism of 2,4-D within Enlist corn and soybeans creates a new route of exposure to residues and metabolites that EPA does not address for listed and non-listed species.

EPA did not assess the metabolites of 2,4-D because the toxicity of and exposure to 2,4-D acid was expected to be higher, and thus pose greater risk concerns, than the metabolites. The 10-state risk assessment *(Addendum to 2,4-D Choline Salt Section 3 Risk assessment: Refined Endangered Species Assessment for Proposed New Uses on Herbicide-Tolerant Corn and Soybean for AR, KS, LA, MN, MS, MO, NE, ND, OK, TN,"* found in Docket ID: EPA-HQ-OPP-2014-0195-2419) for terrestrial organisms assumes that 100% of residues are 2,4-D and that the appropriate toxicity endpoints are relative to the free acid. The acute lethal and reproduction mammalian endpoints used in assessment were 441 mg ae/kg-bw and 55 mg ae/kg-bw/day, respectively. For birds, the acute lethal endpoint was 218.7 mg ae/kg-bw and the reproduction endpoint was 962 mg ae/kg-diet. By comparison, available mammalian data) on the acute lethal endpoint for the metabolite 2,4-dichlorophenol (2,4-DCP) is 580 mg/kg-bw (1.3 times less toxic) (EHC, 1989) and the reproduction data endpoint is 134 mg/kg-bw/day (2.43 times less toxic) (Aoyama et al., 2005). There exist reports for more potent mammalian acute measures of 2,4-dichlorphenol for molten product, e.g. 44 mg/kg (NTIS OTS0534822 1991), but these are not representative of an oral administration expected from its conversion in a biological matrix.

Under the most conservative assumption of degradation, one mole of 2,4-D choline (221.04 g) yields one mole of 2,4-dichlorophenol (163.0 g) for a mass ratio of 0.738. Consequently, the conversion of mass to 2,4-dichlorophenol is about 74% of the corresponding residue assumption for 2,4-D ae on the field. However, data submitted to the Agency and reviewed by the Health Effects Division (HED)[USEPA 2011, D384441 Summary of Analytical Chemistry and Residue Data for Use of 2,4-D Choline in/on Herbicide Tolerant Field Corn Containing the Aryloxyalkanoate Dioxygenase-1 (ADD-1) Gene. Health Effects Division, Office of Pesticide Programs, Environmental Protection Agency", found in Docket ID: EPA-HQ-OPP-2014-0195-0037; USEPA 2013, D400085 Summary of Analytical Chemistry and Residue Data for Use of 2,4-D Choline in/on Herbicide Tolerant Soybeans Containing the

Aryloxyalkanoate Dioxygenase-12 (AAD-12) Gene. Health Effects Division, Office of Pesticide Programs, Environmental Protection Agency, found in Docket ID: EPA-HQ-OPP-2014-0195-0005] on soybean and corn indicated that no more than 18.4% of recoverable residues were 2,4-dichlorophenol and its conjugates in forage, and no more than 9.15% in seed (corn was non-detect).

An example of the impacts of these findings to a risk assessment can be seen with the Indiana bat. Assuming that 2,4-D choline salt has been converted to 2,4-dichlorophenol (plus conjugates) at a rate of 18.4%, the exposure value (excluding any differences in absorption or metabolism in the insect prey) would be 18.4% of the assessment for 2,4-D choline. Toxicity values would be lower by 9.36 for acute toxicity and higher by a factor of 2.43 for reproduction. Therefore, the acute RQ, under the most conservative approach would be:

2,4-dichlorophenol acute RQ assuming total conversion of 2,4-D to 2,4-dichlorophenol:

(RQ for 2,4-D choline 0.06) (1/1.33)(0.184) = 0.008

2,4-dichlorpophenol reproduction RQ assuming total conversion of 2,4-D to 2,4-dichlorophenol:

(RQ for 2,4-D choline a.e.0.47) (1/2.43)(0.184) = 0.036

Both the acute and chronic RQ are below levels of concern (acute LOC = 0.1; chronic LOC = 1). This analysis does not consider the potential for differential in absorption of plant associated 2,4-dichlorophenol and its conjugates. Pascal-Lorber et al. (2012) compared the metabolic fate of [(14)C]-DCP, [(14)C]-residues from radish plants, and purified [(14)C]-DCP-(acetyl)glucose following oral administration in rats. These authors found that rat absorption of plant-associated 2,4-dichlorophenol metabolites was lower from the plant matrix than plant-free conjugates and DCP itself.

The combined effects of lower toxicity and limited residues in corn and soybean forage and seed results in risk quotients for the in-plant degradates that are well below levels of concern. Assuming all exposures as parent 2,4-D choline or its acid equivalent remains the most conservative approach.

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Exhibit D

EPA Plans Response To IARC Glyphosate Finding . . . But Not Just Yet

By: Eric Sfiligoj | April 6, 2015

When news broke that the International Agency for Research on Cancer (IARC) had classified the **herbicide glyphosate as a "probable carcinogenic"** based upon data from some (but not all) research papers on the subject, the Internet and traditional news media went into overdrive with comments, points and counterpoints. In addition, reactions from special interest groups, independent researchers, growers and big crop protection product suppliers such as Monsanto flew fast and furious for several days after the initial announcement. Indeed, in last week's *CropLife* enewsletter, **we looked more closely at this topic (although in a decidedly light-hearted manner).**

Given this outcry for and against continued glyphosate use in agriculture and the consumer market, one important voice has remained missing – the EPA. As the gatekeeper/official researcher into the safety of products used by agriculture, the agency carries quite a bit of regulatory weight in the grand scheme of things.

Yet, when pressed for some comment, EPA has not been very forceful. "In 1991, EPA concluded that glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans) based on a lack of convincing carcinogenicity evidence and considering the criteria in EPA Guidelines for classifying a carcinogen," said the agency in a released statement in early April. "Since then, EPA has monitored emerging research on the carcinogenicity of glyphosate."

Still, according to Carissa Cyran, chemical review manager for the Office of Pesticide Programs at EPA, the agency has been very active in re-reviewing the question of glyphosate safety to humans. Just last year, EPA reviewed more than 55 epidemiological studies conducted on the possible cancer and non-cancer effects of glyphosate. "Our review concluded that this body of research does not provide evidence to show that glyphosate causes cancer, and it does not warrant any change in EPA's cancer classification for glyphosate," wrote Cyran in an e-mail statement to *CropLife* magazine. "This is the same conclusion reached in 2004 by the United Nations'

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periodically," wrote Cyran. "EPA is aware of the recent IARC report and will address it in detail in the preliminary risk assessment."

So stay tuned. This latest glyphosate safety debate is clearly just getting warmed up . . .

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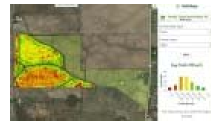

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Exhibit E

International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 236

23 June 2015

IARC Monographs evaluate DDT, lindane, and 2,4-D

Lyon, France, 23 June 2015 - The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization, has evaluated the carcinogenicity of the insecticides gamma-hexachlorocyclohexane (lindane) and dichlorodiphenyltrichloroethane (DDT) and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D).

After thoroughly reviewing the latest available scientific literature, a Working Group of 26 experts from 13 countries convened by the IARC Monographs Programme classified the insecticide lindane as *carcinogenic to humans* (Group 1). There was *sufficient evidence* in humans for the carcinogenicity of lindane for non-Hodgkin lymphoma (NHL).

The insecticide DDT was classified as *probably carcinogenic to humans* (Group 2A), based on *sufficient evidence* that DDT causes cancer in experimental animals and *limited evidence* of its carcinogenicity in humans. Epidemiological studies found positive associations between exposure to DDT and NHL, testicular cancer, and liver cancer. There was also strong experimental evidence that DDT can suppress the immune system and disrupt sex hormones. However, overall there was no association between breast cancer and DDT levels measured in samples of blood or fat.

The herbicide 2,4-D was classified as *possibly carcinogenic to humans* (Group 2B), based on *inadequate evidence* in humans and *limited evidence* in experimental animals. There is strong evidence that 2,4-D induces oxidative stress, a mechanism that can operate in humans, and moderate evidence that 2,4-D causes immunosuppression, based on in vivo and in vitro studies. However, epidemiological studies did not find strong or consistent increases in risk of NHL or other cancers in relation to 2,4-D exposure.

A summary of the final evaluations is available online in *The Lancet Oncology*, and the detailed assessments will be published as Volume 113 of the IARC Monographs.

Lindane has been used extensively for insect control, including in agriculture and for treatment of human lice and scabies. High exposures have occurred among agricultural workers and pesticide applicators; however, the use of lindane is now banned or restricted in most countries. Large epidemiological studies of agricultural exposures in the USA and Canada showed a 60% increased risk of NHL in those exposed to lindane.

DDT was introduced for the control of insect-borne diseases during the Second World War and was later applied widely to eradicate malaria and in agriculture. Although most uses of DDT were banned from the 1970s, DDT and its breakdown products are highly persistent and can be found in the environment and in animal and human tissues throughout the world. Exposure to DDT still occurs, mainly through diet. The remaining and essential use of DDT is for disease vector control, mainly for malaria. This use is strictly restricted under the Stockholm Convention.

Since its introduction in 1945, 2,4-D has been widely used to control weeds in agriculture, forestry, and urban and residential settings. Occupational exposures to 2,4-D can occur during manufacturing and application, and the general population can be exposed through food, water, dust, or residential application, and during spraying.

IARC Monographs evaluate DDT, lindane, and 2,4-D

Note to the Editor:

What does the classification mean in terms of risk?
The classification indicates the *strength of the evidence* that a substance or agent causes cancer. The Monographs Programme seeks to identify cancer hazards, meaning the potential for the exposure to cause cancer. However, it does not indicate the *level of risk* associated with exposure. The cancer risk associated with substances or agents assigned the same classification may be very different, depending on factors such as the type and extent of exposure and the strength of the effect of the agent.

What is the difference between risk and hazard?
The IARC Monographs Programme evaluates cancer hazards but not the risks associated with exposure. An agent is considered a *cancer hazard* if it is capable of causing cancer under some circumstances. *Risk* measures the probability that cancer will occur, taking into account the level of exposure to the agent. The distinction between *hazard* and *risk* is important, and the Monographs Programme identifies cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

Read the *IARC Monographs* Q&A

http://www.iarc.fr/en/media-centre/iarcnews/pdf/Monographs-Q&A.pdf

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The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships. If you wish your name to be removed from our press release e-mailing list, please write to com@iarc.fr.

Exhibit F

Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid

In June, 2015, 26 experts from 13 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of the insecticides lindane and 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT), and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). These assessments will be published as Volume 113 of the IARC Monographs.[1]

The insecticide lindane was classified as "carcinogenic to humans" (Group 1). Lindane, the γ-isomer of hexachlorocyclohexane, has been used extensively for insect control in agriculture and for treatment of human ectoparasites. Occupational exposures have occurred among agricultural workers and pesticide applicators; however, the use of lindane is now banned or restricted in most countries. Lindane is lipophilic, readily absorbed via all routes of exposure, and distributes widely in the body.

Epidemiological cohort and case-control studies of non-Hodgkin lymphoma in several countries provided sufficient evidence in humans for the carcinogenicity of lindane. The US Agricultural Health Study,[2] a large prospective cohort study with detailed exposure assessment, reported statistically significant increases in non-Hodgkin lymphoma risk with increasing occupational exposure to lindane. Population-based case-control studies in the mid-western USA and Canada also reported consistently positive associations.[3,4]

Sufficient evidence in experimental animals for the carcinogenicity of lindane was provided by several studies of dietary administration in mice, with lindane consistently increasing the incidence of benign or malignant liver tumours. There is strong evidence that lindane causes immunosuppressive effects that can operate in humans.

The insecticide DDT was classified as "probably carcinogenic to humans" (Group 2A). DDT was used for the control of insect-borne diseases during World War 2; subsequently it was widely applied to eradicate malaria and also used in agriculture. Although most uses of DDT apart from disease vector control were banned from the 1970s, human exposure to DDT and to its metabolite 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene (DDE) still occurs, mainly as a consequence of biological persistence leading to exposure through diet. DDT is readily absorbed and is distributed in the body by lymphatic and blood circulation, with a preference for lipid-rich tissues.

Associations between cancer and exposure to DDT have been investigated in more than 100 cohort and case-control studies from diverse countries. Nested and population-based case-control studies in China reported strong, dose-related associations between liver cancer and blood DDT level after adjustment for potential confounders.[5–7] No excess risk of liver cancer was reported in a historical cohort study[8] of men who sprayed DDT during a malaria-control campaign in Italy. In studies on non-Hodgkin lymphoma, positive associations were reported in several cohort and case-control studies in North America and Europe,[2,9,10] while other studies found no association.[8] Several case-control studies in the USA and Europe reported positive associations between DDT or DDE and testicular cancer, including a large case-control study[11] nested in a US military cohort. Although more than 40 studies conducted since 1993 were reviewed, no clear association was found between breast cancer and DDT or DDE measured in samples of blood or adipose taken in adulthood; however, the possible importance of early-life exposure to DDT remains unresolved. Studies on non-Hodgkin lymphoma and cancers of the liver and testis provided limited evidence in humans for the carcinogenicity of DDT.

Numerous studies in mice, rats, and hamsters (mainly oral administration) provided sufficient evidence in experimental animals for the carcinogenicity of DDT and its metabolites DDE and 1-chloro-4-[2,2-dichloro-1-(4-chlorophenyl) ethyl]benzene (DDD). In mice, 12 studies gave positive results, some for multiple tumour sites, with DDT consistently increasing the incidence of benign and malignant liver tumours; lymphoma incidence was also increased in three studies. In rats, DDT increased the incidence of benign and malignant liver tumours in four studies. In hamsters, DDT significantly increased the incidence of adrenal cortex adenoma in two studies. In rodents, the metabolites DDE and DDD induced liver tumours in two studies each.

There is strong evidence that DDT affects several mechanisms that can operate in humans. Immunosuppression has been consistently observed in numerous experimental systems, including human cells in vitro. DDT, DDD, and DDE increased oxidative stress in human peripheral blood mononuclear cells and stimulated human colon cancer and liver cancer cell proliferation in vitro and in xenografted mice. Oestrogenic effects and androgen-receptor antagonism were consistently observed in numerous experimental systems including human cells in vitro.[12] Anti-oestrogens blocked oestrogenic effects of DDT in human breast cancer cells and in mice.[13] Progesterone receptor activation

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Oct 6–13, 2015, Volume 114: Red meat and processed meat
Feb 2–9, 2016, Volume 115: Some industrial chemicals

Monograph Working Group Members
M Kogevinas (Spain)—Meeting Chair; M L Larramendy (Argentina); B W Stewart (Australia); T Sanderson (Canada); P Guénel (France); P Cocco (Italy); S Fukushima (Japan); ME Cebrian Garcia [unable to attend]; L T Lopez Carrillo (Mexico); R Vermeulen (Netherlands); S Naidoo (South Africa); T Prapamontol (Thailand); F L Martin [unable to attend]; L Rushton (UK); M Alavanja; M Bosland; R S Chhabra; W Chiu; A De Roos; R Herbert; M La Merrill; D M Reif; D Roy; M T Smith; K Thomas; M Wolff (USA)

Invited Specialists
None

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Observers (non-voting)
J S Bus, J E Goodman, and S A McMaster, for the Industry Task Force II on 2,4-D Research Data

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L Benbrahim-Tallaa; V Bouvard; R Brown; F El Ghissassi; Y Grosse;

N Guha; K Z Guyton; M Korenjak; M Leon; D Loomis; H Mattock; K Straif; J Zavadil

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For **declarations of interests** see http://monographs.iarc.fr/ENG/Meetings/index.php

Of the working group members, LR received an honorarium and travel expenses for providing advice on future epidemiological research to a Scientific Advisory Group on Epidemiology of the European Crop Protection Association and MTS has received payment for consulting and testimony from US law firms and research support from the US Council for Education and Research on Toxics. All other working group members declare no competing interests. The representatives declare no competing interests. Of the observers, JSB is a former Dow Chemical Co employee, owns Dow Chemical Co stock, and is a consultant to the 2,4D Research Data Task Force; JEG has received funding from the 2,4D Research Data Task Force; and SAMM is a consultant to the 2,4D Research Data Task Force. The Industry Task Force II on 2,4-D Research Data (Task Force) is an industry consortium whose members hold registrations for the active ingredient 2,4-D. The Task Force members include Dow AgroSciences LLC, Nufarm Ltd, and Agro-Gor Corporation, a US corporation jointly owned by Albaught Incorporated (USA) and PBI-Gordon Corporation (USA). All members of the IARC/WHO Secretariat declare no competing interests.

was seen in vitro. Evidence of sex-hormone disruption in exposed men and women was unclear.

Since its introduction in 1945, 2,4-D has been widely used to control weeds in agriculture, forestry, and urban and residential settings. Occupational exposures to 2,4-D can occur during manufacturing and application, while the general population can be exposed through food, water, dust, residential application, and during spraying. In humans, 2,4-D is eliminated largely unchanged in the urine.

Cancer risks associated with exposure to 2,4-D have been evaluated in population-based case-control studies and in cohort studies of workers manufacturing and applying pesticides. Due to the potential for confounding, studies involving exposure to mixed herbicides or to herbicides containing dioxin were regarded as uninformative about the carcinogenicity of 2,4-D. Neither a nested case-control analysis[14] of an international cohort of workers who manufacture and spray herbicides nor a historical cohort study[15] of 2,4-D manufacturing workers in the USA found strong or consistent increases in non-Hodgkin lymphoma in relation to 2,4-D exposure, but the latter study gave some indication of increased risk in the highest categories of estimated exposure. Population-based case-control studies of 2,4-D exposure in relation to lymphoma and leukaemia reported mixed results. The Working Group conducted a meta-analysis of 11 studies that showed no association of non-Hodgkin lymphoma with ever-exposure to 2,4-D, although the results appeared to be sensitive to whether the studies adjusted for other pesticides. The consensus of the Working Group was that there is inadequate evidence in humans for the carcinogenicity of 2,4-D, although a substantial minority considered that the evidence was limited.

The carcinogenicity of 2,4-D has been assessed in multiple rodent bioassays and in an observational study of pet dogs. In female mice, single subcutaneous injections of the isooctyl ester of 2,4-D increased the incidence of reticulum-cell sarcoma.[16] In male rats, 2,4-D in the diet induced a positive trend in the incidence of rare brain astrocytomas.[17] The Working Group concluded that there was limited evidence in experimental animals for the carcinogenicity of 2,4-D due to methodological concerns regarding the positive studies, although a substantial minority judged the evidence to be sufficient.

Mechanistic studies provided strong evidence that 2,4-D induces oxidative stress that can operate in humans and moderate evidence that 2,4-D causes immunosuppression, based on in-vivo and in-vitro studies.

In considering all the relevant scientific data, the Working Group classified 2,4-D as "possibly carcinogenic to humans" (Group 2B).

We declare no competing interests.

Dana Loomis, Kathryn Guyton, Yann Grosse, Fatiha El Ghissasi, Véronique Bouvard, Lamia Benbrahim-Tallaa, Neela Guha, Heidi Mattock, Kurt Straif, on behalf of the International Agency for Research on Cancer Monograph Working Group, IARC, Lyon, France

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Exhibit G

News / Watchdog

EPA tosses aside safety data, says Dow pesticide for GMOs won't harm people

By **Patricia Callahan · Contact Reporter**
Chicago Tribune

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How the EPA cleared the way for Dow to revive a worrisome old pesticide for new GMO crops.

DECEMBER 8, 2015, 10:13 PM

When Monsanto genetically engineered corn and soybeans to make them immune to its best-selling weedkiller, the company pitched the technology as a way to reduce overall use of herbicides and usher in an environmentally friendly era of farming.

Instead of relying on older, more harmful chemicals, farmers could douse their fields with Roundup, a product that Monsanto once advertised as less toxic than table salt.

Two decades later, overuse of Roundup has spawned weeds that can survive spraying to grow 8 feet tall with stems as thick as baseball bats. To kill those so-called superweeds, chemical giants are giving the next wave of genetically modified crops immunity to the weedkillers of generations past.

The technology that was supposed to make those older herbicides obsolete soon could make it possible for farmers to use a lot more.

Article continues below ↓

For use on its new genetically engineered corn and soybeans, Dow Chemical Co. is reviving 2,4-D, a World War II-era chemical linked to cancer and other health problems.

If these crops are widely adopted, the government's maximum-exposure projections show that U.S. children ages 1 to 12 could consume levels of 2,4-D that the World Health Organization, Russia, Australia, South Korea, Canada, Brazil and China consider unsafe.

[An Iowa farmer depends on pesticides. His son asks: Is there a better way? ***Read Part 2****]*

The U.S. Environmental Protection Agency had considered that exposure dangerous for decades as well. But the Obama administration's EPA now says it is safe to allow 41 times more 2,4-D into the American diet than before he took office.

To reach that conclusion, the Tribune found, the agency's scientists changed their analysis of a pivotal rat study by Dow, tossing aside signs of kidney trouble that Dow researchers said were caused by 2,4-D.

The EPA scientists who revised that crucial document were persuaded by a Canadian government toxicologist who decided that Dow — a company that has a $1 billion product at stake — had been overly cautious in flagging kidney abnormalities that she deemed insignificant.

When Dow later published this study, the company's scientists likewise dismissed their earlier concerns and changed the most important measure of the chemical's toxicity so it agreed with the EPA's less stringent view.

These decisions paved the way for the EPA to approve Dow's weedkiller Enlist Duo last year and reassure the public that a surge in 2,4-D use wouldn't hurt anyone.

Girding that reassurance are two calculations: How much of the herbicide is safe for human health, and how much will Americans wind up consuming? There are ways to tweak each of those risk calculations. With 2,4-D, the Tribune found, the EPA's math favored a dramatic increase in the weedkiller.

Article continues below ↓

Federal law has required the EPA to protect children from pesticides — chemicals that kill weeds, insects or other harmful organisms — since a National Research Council panel warned lawmakers in the 1990s that exposing fetuses and young kids to these compounds can cause lifelong damage at doses that wouldn't hurt their parents.

Dr. Philip Landrigan, the pediatrician who chaired that panel, is so alarmed by the potential spike in children's exposure to 2,4-D that for the last year he has urged EPA Administrator Gina McCarthy to reject the "notoriously toxic herbicide." He is calling for the federal National Toxicology Program to assess the safety of the mix of weedkillers that would be used on new genetically modified crops.

When Landrigan learned from the Tribune that EPA and Dow scientists had changed their minds about kidney anomalies found in exposed rats, he was shocked.

"If the tables were turned, and a group of scientists published a paper showing some adverse effect from 2,4-D, I have no doubt that Dow would say a second and third study were needed," said Landrigan, whose research on childhood lead exposure helped prompt the removal of lead from gasoline and paint. "And yet, Dow is saying we need to trust this one study where results were reinterpreted midstream. There's reason to raise doubt here."

Dow said 2,4-D is safe and is one of the most extensively studied pesticides in history. James Bus, a

former Dow toxicologist who worked on the company's recent rat study, said the EPA's evaluation of 2,4-D relies on state-of-the-art science and "stands as an example of how it should be done."

"We know from 70 years of exposure that 2,4-D has not presented health problems," Bus said. Studies that suggest such a link are flawed, and increased use will not put anyone at risk, he added.

For its part, the EPA said its scientific vetting ensures that any pesticide residues left in food and water won't cause harm. The Dow rat study reveals that 2,4-D is less toxic to people than once thought, agency officials say.

"It is EPA's understanding that other governments do agree with our interpretation of the new study, but have not yet incorporated the results into their 2,4-D reviews," EPA spokeswoman Cathy Milbourn said in a written statement.

In a surprise move last week, the EPA asked the 9th U.S. Circuit Court of Appeals to vacate the agency's approval so its scientists could review new data. But EPA officials made it clear they don't intend to bar the product permanently.

The holdup has nothing to do with human health. Enlist Duo combines 2,4-D and glyphosate, the main ingredient in Roundup, and the agency said it wanted to iron out concerns that the two chemicals combined are more toxic to endangered plants than either of the chemicals separately.

As far as people's health is concerned, though, the agency maintains that Enlist Duo is perfectly safe. Even if American farmers spray 2,4-D on every acre of corn and soybeans — crops that serve as the building blocks of processed foods and fatten farm animals — it still won't harm consumers, the EPA said.

So confident is Dow that the agency's concerns about endangered plants can be resolved quickly that the title of its news release last week read: "Dow Expects Enlist Duo to be Available for the 2016 U.S. Crop Season."

With so many farmers in America planting genetically modified crops, the potential market for Dow's product is huge. Today 94 percent of soybeans and 89 percent of corn planted in the U.S. are genetically engineered to survive herbicides, primarily the glyphosate in Roundup.

No one is comparing glyphosate to table salt anymore, though, with the WHO's cancer research agency now labeling it a probable carcinogen. And no one is hailing it as an agricultural savior.

More than 60 million acres of U.S. cropland are being choked by weeds that glyphosate can't kill. In response, chemical companies and federal regulators are advising farmers not to substitute one weedkiller for another but to add more.

Even some scientists who have spent their professional lives eradicating weeds oppose the new genetically modified crops and the chemical future they foreshadow.

"Those herbicide increases are not OK," said David Mortensen, a professor of weed and applied plant ecology at Pennsylvania State University. "To me, that is unconscionable that we can be OK with that, and I'm not an anti-chemical radical."

How much is too much?

Many people complain that eating genetically modified food could endanger their health. But it's the weedkillers used on genetically modified crops, not the corn and soy, that scientists have repeatedly found to cause harm.

Herbicides linger in the water Americans drink, in the air they breathe and on the foods they eat. Children are especially vulnerable because they take in more food, water and air, relative to their weight, than adults.

That's why scientists study weedkillers so closely and why regulators scrutinize them more heavily than other industrial chemicals.

Article continues below ↓

The fact that 2,4-D was a main component of the Vietnam War-era defoliant Agent Orange made the chemical infamous, even though it was dioxin contamination of a different ingredient that brought harm to troops and villagers.

Over the years, federal and university researchers showed 2,4-D was worrisome on its own. Studies found increased odds of developing non-Hodgkin lymphoma, hypothyroidism and Parkinson's disease among people who used the chemical as part of their jobs. In June, the WHO's cancer research agency ruled that 2,4-D is a possible carcinogen.

But EPA scientists aren't convinced that 2,4-D causes any of those diseases because other studies reached different conclusions.

Though it wasn't widely used on corn and soybeans, 2,4-D has been a go-to chemical for wheat growers, ranchers and golf course groundskeepers. When the EPA in the early 2000s revisited the safety of 2,4-D as part of a wider review of pesticides long on the market, the goal was to determine from animal testing how much 2,4-D people could safely consume.

Such tests are carried out or commissioned by chemical-makers, even though they have a vested interest in the results.

The EPA relied on a 1995 Dow study that found rats dosed daily with 75 milligrams of pure 2,4-D per

kilogram of body weight (or mg/kg) over a two-year period gained less weight and experienced changes in kidney, thyroid, liver, lung, reproductive organ and blood chemistry measures compared with untreated rats.

Rats that consumed the next lowest dose — 5 mg/kg — showed no ill effects. This is called the "no observed adverse effect level," and it's the most important measure in a pesticide toxicity study.

Next came a series of math exercises. As they always do, EPA officials divided that dose by a factor of 100 to account for the fact that rats and humans are different and some people have heightened sensitivity to chemicals.

Since the mid-1990s, the EPA has been required to divide again — this time by a factor of 10 — because Landrigan's panel found children are more vulnerable than adults. This protection may be removed only if "such margin will be safe for infants and children."

In the case of 2,4-D, the EPA kept it in place because its scientists couldn't tell whether 2,4-D disrupts hormones, immunity and neurological development.

When the dividing was done, the EPA under President George W. Bush set the acceptable daily intake of 2,4-D at 0.005 mg/kg. Separate calculations showed that nobody was consuming too much, the EPA said at the time.

That same year, 2005, the EPA ordered the manufacturers to conduct two new studies that could answer the remaining questions about safety — research that ultimately would lead to the weakening of consumer protections.

One study was to expose adult rats and two generations of offspring to 2,4-D while looking for immune system problems, thyroid effects and toxicity in other organs. Another would scrutinize neurological development in offspring.

But with the EPA's permission, Dow rolled the studies into one and halted what would become the most important evaluation of 2,4-D after breeding just one generation of rats.

Article continues below ↓

Dow's study design, which called for breeding a second generation only if certain problems were evident in the first, was crafted by a committee of the ILSI Health and Environmental Sciences Institute, a nonprofit that receives much of its funding from chemical, food and pharmaceutical companies.

The committee included scientists from pesticide giants Dow, Syngenta, Bayer and DuPont, as well as one from Exponent, a scientific consulting firm. In addition to providing regulatory help to pesticide-makers and other companies, Exponent is "the go-to firm at the top of the pyramid" for companies

that face a lawsuit, a product recall or a government crackdown, Exponent's financial chief told Wall Street analysts this year.

One of the few EPA members on the committee later went to work for Exponent. Bus, who helped lead the Dow study, joined Exponent after he retired; he still consults for Dow on 2,4-D.

Officials from the EPA and Dow say the committee's study design rigorously assesses many potential toxic effects from conception to adulthood while sacrificing fewer animals. The Organization for Economic Cooperation and Development, consisting of 34 countries, agrees and uses it as an international testing guideline.

But Paul Foster, a top toxicologist at the National Toxicology Program, said the study design has such "serious scientific weaknesses" that his arm of the federal government won't use it in its research. For example, the Dow study exposed rats to 2,4-D for four weeks before they mated. Foster said dosing should last 10 weeks to cover the entire time it takes rats to make sperm.

Moreover, though a 2011 analysis of 498 studies concluded the second generation "will very rarely provide critical information," Foster said it's important to find those rare instances of harm.

"Everyone wants to use the minimum number of animals to generate quality data, but there comes a time when you don't want to cut the corners too much," Foster said.

Bus said EPA and Canadian regulators, who reviewed data while the study was in progress, decided breeding a second generation wasn't warranted.

In 2010, Bus and his colleagues reported the results in a poster presentation at the Society of Toxicology's annual meeting. By then, Dow's field trials had demonstrated the genetically modified crops were viable, and the march of superweeds foretold potentially big sales.

Article continues below ↓

The poster stated that 2,4-D did not cause immune, reproductive or neurological harm. Some rats experienced thyroid hormone changes, and some males had lighter-weight reproductive organs, but Dow scientists took the position that these effects were not adverse.

But they did find a problem with the kidneys. The poster said exposure-related kidney lesions occurred at a lower dose in male rat offspring than in their parents.

When two EPA scientists examined the Dow data that year, they came to the same conclusion. Both Dow and the EPA decided the no-adverse-effect level was the smallest dose tested in the offspring, an amount equivalent to about 7 mg/kg, records show.

Then something curious happened. The EPA and Dow scientists changed their minds.

More becomes OK

Six months later, the same EPA scientists revised the executive summary of their report, changing the crucial measure of toxicity.

The lesions that Dow scientists found in offspring at 7 mg/kg weren't harmful after all, EPA scientists Linda Taylor and Elizabeth Mendez wrote. They changed the no-adverse-effect level so that it was the same for both the rat offspring and parents: an amount equivalent to 21 mg/kg.

Dana Vogel, who oversees the EPA division that assesses herbicide health effects, told the Tribune the original report by Taylor and Mendez was based on "preliminary data — not the entire study but the first part of the study that came in."

In fact, there was nothing preliminary about the data, and no details were missing. The facts that Taylor and Mendez later cited to justify the change were all part of their original 108-page report, which scrutinized blood test results, organ weights and microscopic analysis at every stage of life.

Their observations were minutely detailed, describing the kidney problem as "a degenerative lesion involving the proximal convoluted tubules in the outer stripe of the outer zone of the medulla, which was multifocal in distribution."

What really led to the change of heart, interviews and an EPA document show, was a phone call from a Canadian pesticide regulator.

Lauri Stachiw was the Canadian government toxicologist who reviewed Dow's data as the study was unfolding. Stachiw told the Tribune she called Taylor and Mendez because she disagreed with their report.

Stachiw noted that Dow researchers found the kidney lesions only in male offspring at that lower dose and classified them as "very slight to slight degeneration" rather than severe. Those rats didn't have heavier kidneys, a different sign of trouble. For true toxicity, Stachiw said, she would expect moderate or severe lesions as well as heavier kidneys in those rats.

Though Dow scientists thought the lesions were harmful, Stachiw said: "I think they were just trying to be as conservative as possible, but being as conservative as possible isn't always correct science."

Stachiw, now retired, added, "If you cut your finger, it's an effect. Is it adverse compared to cutting your finger off? No."

In an interview, Mendez said she and Taylor looked at the data again after Stachiw called. Mendez said they decided the lesions Dow had labeled as toxic effects were actually a healthy response.

"It's a good thing that the kidney is gearing itself up for battle to get rid of the compound from the

body," she said. Taylor declined to comment.

Bus, the Dow consultant, said the company did not influence Stachiw or the EPA. He said Dow was surprised when the EPA revised the no-adverse-effect level.

"We were totally out of the loop," Bus said.

Article continues below ↓

When the Society of Toxicology's journal published the Dow study results in 2013, the article said the kidney lesions in the rat offspring dosed with 7 mg/kg "were judged to be not treatment related."

Bus said he and his colleagues adopted the position of the Canadian and EPA scientists. "It's not uncommon for reviewers to say, 'Wait a minute, we have an alternative interpretation of your data,'" he said. "... I would not have serious disagreement with how they interpreted that data."

Industry-funded researchers have found kidney trouble before in animals consuming low doses of 2,4-D, the Tribune found. An industry group representing Dow and other 2,4-D manufacturers submitted five studies to the EPA in the 1980s that documented kidney abnormalities in rats and mice at doses far lower than the one the agency now is using to set safety levels for people.

EPA scientists and the trade group agreed three decades ago that the kidney was the "target organ for toxicity" with anomalies seen at doses as low as 5 mg/kg, records show.

Bus said of those studies: "Earlier conclusions that might have been interpreted as adverse may not be considered adverse in more modern science."

Asked whether studies should be discounted when they're that old, the National Toxicology Program's Foster said, "You can look at the differences in study quality, but the way we remove kidneys and look at them under a microscope has not changed in the last 60 or 70 years."

The EPA's Mendez said her agency considered the "whole gamut of studies."

When she and Taylor raised the no-adverse-effect level to 21 mg/kg, they paved the way for the agency to reduce consumer protections.

EPA scientists had no remaining questions about the chemical's harmful effects, and there was no longer evidence of the special susceptibility of children because the revised view of the Dow study held that the toxic effects in the offspring occurred at the same dose as in the parents. So, the agency dropped the tenfold child-safety factor.

Rather than dividing the rat dose by 1,000, as it had done a decade ago, the agency divided only by 100, resulting in a far less protective limit. Regulators set the allowable daily intake of 2,4-D for people

at 0.21 mg/kg, 41 times more than the government had previously considered safe.

This was a victory for Dow because the calculations made it easier for the EPA to approve the new uses of 2,4-D the company needed in order to market its genetically modified crops. The agency could tell consumers these new uses wouldn't be harmful.

The Environmental Working Group, a nonprofit that is among those suing the EPA for approving Enlist Duo, scrutinized the Dow study results outlined in the EPA's official human health risk assessment. That document didn't mention that Taylor and Mendez had revised their interpretation.

Even so, a scientist for the nonprofit independently settled on the same measure of toxicity that the EPA and Dow initially had used: 7 mg/kg.

The group concluded that agency officials had "contradicted standard scientific practice" in choosing as their no-adverse-effect level a dose at which rats actually suffered multiple toxic effects — not just the kidney lesions but also the thyroid and reproductive organ changes.

That group also argued that the agency by law must apply the child-safety factor to its risk calculations because the offspring were more susceptible than the parents. Under that reasoning, the allowable daily intake would be 0.007 mg/kg.

The EPA's own worst-case exposure estimates, included in the official human health assessment, found toddlers could wind up consuming three times more than that.

Yet the agency, responding to critics, reassured the public that its scientists had determined that nobody would consume too much, even using the hypothetical limit of 0.007 mg/kg.

When the Tribune asked how that could be possible, the agency said its scientists made additional calculations based on more realistic assumptions of exposure, describing that step as a standard practice.

Those calculations, records show, estimated that toddlers could consume 0.0066 mg/kg of 2,4-D — just four ten-thousandths shy of the hypothetical limit.

The math, once again, worked in 2,4-D's favor.

Article continues below ↓

A chemical future

At last year's Farm Progress Show in the heart of Iowa, lines of farmers gazed at Dow’s vision of the future of American agriculture: rows of lush soybeans and towering corn plants genetically engineered to withstand 2,4-D and glyphosate.

This year, Dow didn't bother to plant those crops for the farm show held in Decatur, Ill. On display instead was an air of inevitability.

Ben Kaehler, Dow AgroSciences' U.S. sales leader, was there to extol the benefits of the crops. But rather than convincing farmers that the technology works, Kaehler tried to persuade them to plant Dow's offerings rather than Monsanto's proposed crops, which are immune to glyphosate and dicamba, a 1960s weedkiller.

The question wasn't whether to plant the next generation of genetically modified crops — it was which of those crops to plant.

On a faux brick wall in the Dow tent, a baseball-style scoreboard pitted Dow against Monsanto. Each inning featured a question about the crops or the different weedkillers, with salespeople revealing the answers one by one. Overhead, a banner beckoned: "Grow your field of dreams."

At that point, the only holdup for Dow was China, a major buyer of U.S. crops. Grain elevators here still are waiting for China's approval before agreeing to handle the new crops.

Now Dow also must address the concerns EPA raised last week about Enlist Duo's effects on endangered plants. An agency scientist noticed that a patent application for the product said it had "synergistic weed control" properties that made glyphosate and 2,4-D "more effective in combination than when applied individually."

Previously, the agency had maintained that the two chemicals were no more toxic together than they were on their own. That's why the health assessment of Dow's weedkiller hinged solely on the new risks posed by 2,4-D. Glyphosate already is widely used on corn and soybeans.

The EPA has asked the appellate court to rescind its approval of Enlist Duo while agency scientists decide whether a bigger no-spray zone is needed near the edge of farm fields. Dow said it's confident the issue can be resolved before spring planting.

The EPA told the Tribune it isn't reopening its human health risk assessment. William Jordan, deputy director of the agency's Office of Pesticide Programs, said the combination of 2,4-D and glyphosate doesn't create added risk for people. Jordan cited tests in which researchers gave large one-time doses of Enlist Duo to rats, rabbits, birds and fish, then monitored the animals for two weeks. There was no increased toxicity from the mixture, he said.

Landrigan, the pediatrician whose work led to the lead-paint ban, is more concerned about the long-term health effects of the chemical mixture. One-time doses and short-term monitoring don't address that.

The EPA said it has no plans to ask Dow for studies that chronically dose rats with the combination of

2,4-D and glyphosate.

For anyone concerned about exposure to toxic weedkillers, a different disclosure in Dow's patent applications may be more telling.

The company's application for its genetically modified corn and soybeans foreshadows the day when weeds develop resistance to glyphosate and 2,4-D. Dow, these records show, envisions adding traits to corn and soybeans so they can survive being sprayed with weedkillers from up to 17 different chemical families.

pcallahan@tribpub.com

Twitter @TribuneTrish

This article is related to: Environmental Science, Animal Research, Endangered Species, Medical Research, U.S. Environmental Protection Agency, Canada, The Pennsylvania State University

Exhibit H

NRDC SWITCHBOARD
Natural Resources Defense Council Staff Blog

Sylvia Fallon's Blog

From bad to worse? - NRDC tells EPA to oppose new Enlist Duo pesticide

Posted July 1, 2014

Earlier this year we told you about how glyphosate – commonly known as Round Up – was responsible for contributing to the dramatic decline in monarch butterflies by eliminating milkweed, the one plant the monarchs depend on to reproduce. Round Up has been so effective that scientists have documented a huge decline in the presence of milkweed in agricultural fields and along with it, a corresponding decline in monarch butterflies. But other types of weeds have actually developed a resistance to glyphosate and no longer respond to the application of this pesticide. Therefore, the chemical companies are looking to address this problem. Naturally, their solution is: Even more pesticides!

Dow Chemical recentlypetitioned the EPA to register a new pesticide that combines glyphosate with another pesticide: 2, 4D. The same company has developed genetically engineered corn and soy that withstand both of these pesticides. This way farmers can douse their fields with two pesticides at once and eliminate any weeds, including those that are resistant to glyphosate, all without harming their crops. . So tell me, what happens when the weeds develop resistance to 2, 4 D?

Anyone can see where this is headed – a snowballing effect of more and more powerful pesticides that threaten both wildlife and human health. This is hardly a sustainable solution. That's why NRDC submitted comments to the EPA highlighting the agency's failure to address the impacts that the combined use of glyphosate and 2, 4 D will have on the environment and on public health.

Several months ago NRDC also filed a petition with EPA to evaluate glyphosate given the impacts it is having on the imperiled monarch population. At a minimum, EPA should not allow the registration of this new cocktail of pesticides until it has conducted that evaluation. Furthermore, there are significant public health concerns with the expanded use of 2, 4D that need to be addressed. But more than anything, EPA needs to acknowledge that going down a path of approving more and more pesticide combinations will not produce not a sustainable or healthy future for anyone. Two wrongs will never make a right.

Comments

Sarah McLean — Jul 1 2014 04:58 PM
Do you have kids? Wouldn't you like them to know a butterfly too?

Deborah Hulsewede — Jul 1 2014 05:07 PM
We rarely see butterflies. Leave them alone.

Chuck Newton — Jul 1 2014 06:58 PM
We don't need Round-Up type pesticides. People overuse and abuse them.

Barbara Sherman — Jul 1 2014 07:28 PM

Stop killing. Stop the Roundup. Now.

Deborah Mohler — Jul 1 2014 10:04 PM
Stop the killing!!! Your killing our butterflies!! What will it be next, our birds, our rabbits, squirrels, our pets. Stop the use of Round-Up and stronger pesticides!!!

Linda Lyerly — Jul 1 2014 10:07 PM
We need to plant milkweed. Are there many varieties ? But even so why does society have to face disaster before we see the Light? And make a change??!

Barbara Monroe — Jul 2 2014 12:15 AM
Please save the butterflies, the bees and the birds!

Christina Bombard — Jul 2 2014 01:16 AM
Stop round-up! The end of pollinators marks the end of food!

yolanda rosales — Jul 2 2014 02:54 AM
Poisons kill us all. Greed is poison. Everything dies.

Rene Robert — Jul 2 2014 07:02 AM
Protect God's Creation!

Jen Lopez — Jul 2 2014 08:10 AM
Roundup is not only killing butterflies, it's toxic to humans. Look at the rise in deadly cancers.

Leslie Rittenberg — Jul 2 2014 11:19 AM
Find something safer please.

Jacqui Melman — Jul 2 2014 11:31 AM
Please stop using chemicals!!! You are destroying nature and our livelihood here on earth. You should be ashamed of yourself and how little respect you have for life and this planet!!!

Kathleen Kovacs — Jul 2 2014 05:09 PM
totally against life in it self Im pleased I never trusted or used roundup .

READ MORE BELOW

go ahead and do us all a favor and have a roundup martini night at dow industries why not your here on earth , what you wouldn't want the side affects, well earth doesn't either

Annie Connros — Jul 2 2014 06:30 PM
Please change your chemicals to something that will not bite the hand that feeds us!
We will crush you. You will go out of business. We will not buy the product and we will spread the word through social media, friends and family.

Pamela Roberts — Jul 2 2014 10:58 PM
These pesticides are strong and indiscriminate,. The monarch is a visible victim; there are so many other species we do not notice that are also disappearing. Shame on us for putting greed first.

Guthrum — Jul 5 2014 01:53 PM
Could you give me some alternatives to Round Up? Our yard has quite a few different kinds of weeds, but mainly Johnson grass, crab grass, and clover. I use Weed and Feed, and Roundup. I don't want weeds in our lawn. I also have a problem with weeds growing under the deck, so I spray there also. Everyone around here does it. So give me a good, effective alternative. We also have fire ants, but we put out some kind of powder in their nests that kills them. We do have plenty of butterflies. Now if you can tell me what to use for Japanese beetles.

Jane Bonkoski — Jul 8 2014 11:14 AM
Decency and Compassion

Kerstin Kvisler — Jul 9 2014 08:09 AM
Save us all from highly toxical Glyphosate now!

Donna Franklin — Jul 9 2014 01:00 PM
When will they stop? will they wait until all the animals are extinct? Stop the pesticides! The money won't buy or bring back our precious animals.

Comments are closed for this post.

Exhibit I

NRDC SWITCHBOARD
Natural Resources Defense Council Staff Blog

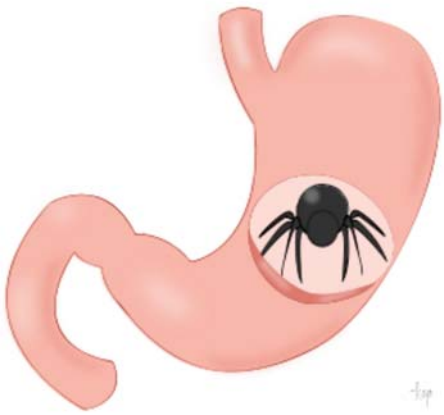
Kristi Pullen's Blog

Question answered - EPA approves Enlist Duo

Posted October 15, 2014

Despite ample evidence illustrating the ability of 2,4-D (also known as 2,4-dichlorophenoxyacetic acid) to impact the delicately balanced thyroid system, and the uncertainty associated with the levels at which humans might be exposed to its increased use, the Environmental Protection Agency (EPA) announced its approval of Enlist Duo™ today.

As I detailed in my last blogpost, Enlist Duo™ is the chemical combination of two herbicides: 2,4-D and glyphosate (the active ingredient in "Roundup®"). Intended for use with corn and soy that have been genetically modified to be resistant to both herbicides, Enlist Duo™ is the chemical industry solution to our herbicide resistance problem. In other words, to stop the growth of weeds that are resistant to single herbicides, farmers should just use more herbicide. To continue the metaphor from my last post, by approving Enlist Duo™, EPA relied on the flawed logic of solving a problem with a problem, and let the old lady swallow the spider.



As NRDC has commented in the past (see our comments to USDA and EPA), Enlist Duo use has the potential to increase human exposure to 2,4-D - a worrisome trait given that scientific studies suggest that exposure to 2,4-D could increase the risk of birth defects, decrease fertility, and lead to improper thyroid functioning (normal thyroid function is critical for brain development and other metabolic processes).

Enlist Duo™ should not have been approved for a host of reasons, including some that are directly relevant to human health, like:

> Multiple streams of evidence (including molecular, animal, and epidemiologic studies) demonstrating adverse impacts of 2,4-D on the thyroid;
>
> High potential for infants, children, and women of child-bearing age to be exposed to Enlist Duo™ via air, food, and water;
>
> The complete absence of information on how the combination of 2,4-D and glyphosate will impact human and ecological health (including habitats for the iconic Monarch butterfly); and
>
> EPA's hopelessly out-of-date health risk assessment for glyphosate (the last EPA human health risk assessment for glyphosate was completed over 21 years ago).

In response to EPA's inadequately protective approval decision, NRDC immediately filed a lawsuit challenging EPA's decision to register Enlist Duo™. By holding EPA accountable for its mission "to protect human health and the environment", the NRDC suit seeks to protect the people, places, and populations (including Monarchs) that we all know and love.

Exhibit J

NATURAL RESOURCES DEFENSE COUNCIL

Press Release

Main page | Archive

FOR IMMEDIATE RELEASE

Press contact: Jay Branegan, 202-513-6263, jbranegan@nrdc.org or Elizabeth Heyd, 202-289-2424, eheyd@nrdc.org
If you are not a member of the press, please write to us at nrdcinfo@nrdc.org or see our contact page

NRDC Sues EPA to Block New Pesticide That Threatens Monarch Butterflies, Human Health

WASHINGTON (October 15, 2014)—The Natural Resources Defense Council today filed suit to block the use of a powerful, newly approved weed killer that will wreak further destruction on monarch butterfly populations already devastated by agricultural chemicals and poses risks to human health.

The suit was filed in the D.C. Circuit court immediately after the Environmental Protection Agency approved the use of "Enlist Duo," a combination of two herbicides: glyphosate (initially marketed as Roundup) and 2,4-D, an older, toxic herbicide. Enlist Duo is intended for use on corn and soybeans genetically modified to be resistant to this chemical cocktail. Glyphosate, the most widely used weed killer in the country, is the chief cause of the decline of the monarchs, and scientists have raised serious questions about 2,4-D's impact on human health.

"This weed killer is more bad news for monarch butterflies, whose migrating population has dropped by more than 90 percent in recent years because glyphosate has wiped out the milkweed they need to survive," said Sylvia Fallon, a senior scientist at NRDC. "EPA completely ignored the impact on monarchs when it granted this new approval, and seriously underestimated the toxicity for people."

Citing the devastating impact on monarchs, NRDC earlier this year filed an emergency petition with EPA to restrict glyphosate, which has soared ten-fold in use since biotech giant Monsanto's introduction of glyphosate-resistant "Roundup Ready" crops in the 1990s. These crops have been widely adopted and as a result, farmers can drench their fields with the weed killer, in the process destroying vast amounts of native milkweed, the only food that monarch larvae can eat.

The heavy use over the years has resulted in the rise of glyphosate-resistant "super weeds" (not including milkweed, however). Chemical maker Dow AgroSciences responded by developing new corn and soybeans resistant to both glyphosate and 2,4-D. The Agriculture Department predicts Enlist Duo could result in as much as a six-fold increase in the use of 2,4-D, a herbicide developed in the 1940s that has been linked to health impacts in humans, including decreased fertility, birth defects and thyroid problems. Dow won approval to use Enlist Duo over more of the growing season than has been authorized for 2,4-D alone, which could mean wider human exposure.

"Because of its documented impacts on the thyroid, a critical organ for brain development, infants and children are at especially high risk from adverse impacts of 2,4-D exposure," said Kristi Pullen, an NRDC staff scientist. People can be exposed to 2,4-D in numerous ways, including contaminated food, drinking water, or breast milk (for nursing infants), and through inhalation of pesticide particles released during use on nearby fields.

"Solving one pesticide's problem by adding another puts us on a completely unsustainable path," Fallon said. "EPA has started a snowballing effect of more and more powerful pesticides that threaten both wildlife and human health."

The monarch butterfly, which makes a unique annual migration from Mexico through the Midwest and eastern U.S. to Canada and back, has been in decline since Monsanto introduced transgenic crops. Where once as many as a billion were recorded at their winter refuge in the Mexican mountains, this year only about 33 million returned, a record low. Deforestation and climate change have contributed to the crisis, experts say, but the massive loss of milkweed habitat is the main culprit.

In addition to seeking restrictions on the use of herbicides that destroy milkweed, NRDC is working to develop "butterfly highways" by promoting the planting of milkweed along the monarchs' migration routes.

For background on monarchs and herbicides, see Sylvia's blog: http://switchboard.nrdc.org/blogs/sfallon/epa_approves_new_pesticide_com.html

For background on 2,4-D, see Kristi Pullen's blog: http://switchboard.nrdc.org/blogs/kpullen/question_answered_epa_approves.html

Exhibit K

NRDC SWITCHBOARD
Natural Resources Defense Council Staff Blog

Sylvia Fallon's Blog
The Fight

Widens: NRDC challenges the approval of the pesticide combination Enlist Duo in nine more states

Posted April 20, 2015

Back in October, EPA approved a new pesticide, Enlist Duo, which combines glyphosate (commonly known as Roundup) with another powerful weed killer called 2,4 D in six states (Illinois, Indiana, Iowa, Ohio, South Dakota and Wisconsin). NRDC filed a lawsuit challenging EPA's approval of Enlist Duo because it will wreak further destruction on monarch butterfly populations already devastated by agricultural chemicals and because the pesticide poses risks to human health. However, rather than acknowledge the shortcomings of its approval of Enlist Duo, the EPA recently expanded its approval to an additional nine states (Arkansas, Kansas, Louisiana, Minnesota, Missouri, Mississippi, Nebraska, Oklahoma and North Dakota). Today, NRDC is challenging that decision as well.

Enlist Duo is designed to be used in conjunction with genetically modified corn and soy crops that have been engineered to withstand the application of the powerful pesticide, much like how its predecessor Roundup was designed to be used on genetically modified Roundup Ready crops. However, the widespread use of Roundup (glyphosate) over the years has led to the widespread destruction of milkweed, a native wildflower that monarch caterpillars depend on. The monarch population that famously migrates across the US each year has dropped by 90% since the late 1990s when Roundup Ready crops were adopted. Although large quantities of milkweed have largely been eliminated, other weeds have developed a resistance to glyphosate and are now known as "super weeds." Dow AgroSciences has responded by developing new genetically engineered corn and soybeans that are resistant to *both* glyphosate and 2,4-D. The US Department of Agriculture predicts Enlist Duo could result in as much as a six-fold increase in the use of 2,4-D, a herbicide developed in the 1940s that has been linked to health impacts in humans, including decreased fertility, birth defects and thyroid problems. Additionally, glyphosate, the other ingredient in Enlist Duo, was recently classified as a "probable carcinogen" by the World Health Organization.

EPA's mission is to safeguard the environment and human health - however, its decision to approve Enlist Duo does neither. Enlist Duo will only further contribute to the dramatic decline of monarch butterflies and poses significant risks to human health. The approval of Enlist Duo - and its expansion across the US - is a step in the wrong direction for wildlife, for farmers and for public health. We need to get off the unsustainable path of increasingly toxic pesticides and move in the direction of truly sustainable farming solutions.

Photo by Wikimedia user Quarti, used under Creative Commons licensing.

Comments

Barbara Kartak — Apr 24 2015 09:16 AM

Thank you for keeping myself and others informed about this new pesticide's effects, and for going to court for us and creatures like the monarch, to keep us from the sort/long-range harmful effects.
I am not much of a scientist, but I can read, reflect and understand, plus donate some necessary monies to enable you to do your important work. I pray for your success, which is the world's.

Joan Porter — Apr 24 2015 09:29 AM

People seem to forget. When a species is poisoned by something like round-up, it isn't just that species. It is every creature that eats that species as part of its food chain. For example, when you kill bees, you kill bees you also kill the birds that eat them and the cats that eat the birds.

Andrea Scully — Apr 24 2015 10:32 AM

Thank you for this action--On behalf of us all.

Now, how do we help you enroll the help it takes getting this story out, beyond your mailing list; where is our energy best spent? E.g., what's it take to get it in print and online to reach those who care? [beside us working on our basic social media skills so we can pitch in]

Comments are closed for this post.

Exhibit L

NRDC SWITCHBOARD
Natural Resources Defense Council Staff Blog

Sylvia Fallon's Blog

EPA asks to take next generation pesticide Enlist Duo off the market

Posted November 25, 2015

In a striking reversal, the EPA has asked a court to revoke the agency's registration of Enlist Duo, the next generation herbicide that poses threats to both monarch butterflies and human health. EPA initially approved Enlist Duo for uses in six states in October of 2014, and NRDC and other groups promptly challenged the decision in court. Enlist Duo is a combination herbicide that contains both glyphosate (the same active ingredient as in Roundup) and 2,4-D. In making its decision, the EPA says that further consideration of Enlist Duo revealed that the synergistic effects of the two chemicals may be more potent than it had initially realized and therefore, the instructions for use that EPA had previously approved may not be protective enough.

This decision is good news for monarch butterflies as well as public health. NRDC has argued that Enlist Duo will continue to eliminate milkweed, a native wildflower that is the sole food source for monarch caterpillars, and that the pesticide poses health risks to people. In fact, shortly before EPA expanded its registration of Enlist Duo to nine addition states, an international panel of experts classified glyphosate and 2,4-D as probable and possible carcinogens respectively. Furthermore, Enlist Duo, which was created because several varieties of superweeds have developed resistance to glyphosate alone, just escalates a never ending chemical arms race that only leads us towards a more toxic and unsustainable future.

It is troubling that EPA did not adequately assess the toxicity of Enlist Duo before approving its use, which raises major concerns about the agency's regulatory process. For EPA to abandon its defense of the pesticide and ask the court to invalidate the agency's earlier decision is a striking admission of error. Also troubling is that it's possible the EPA will simply impose different buffer requirements on Enlist Duo and then re-issue a new registration. The agency has not indicated that it will address Enlist Duo's impact on monarch butterflies or reconsider the health impacts of the combination pesticide, but if the court grants EPA's request to vacate the registration, the agency will have the ability to do both. And, in fact, if EPA doesn't address the effects of Enlist Duo on monarchs and human health, then it knows that it may simply be facing another lawsuit. This will be EPA's chance to get it right.

In re-evaluating Enlist Duo, the EPA is facing a clear choice: do we want a future of increasingly toxic pesticide use? Or do we want to reject the pesticide treadmill and encourage sustainable solutions that will benefit farms, people, and the environment?

Comments

Jay Branegan — Nov 30 2015 12:28 PM

Kudos to NRDC for getting EPA's attention by filing suit against Enlist Duo! Keep up the pressure. The last thing we need is the spewing of more chemicals--especially toxic, long-lived ones like 2,4-D--into the air we breathe and the water we drink. EPA needs to get its priorities straight. AFter all, it's called the ENVIRONMENTAL Protection Agency, not the Agrochemical Industry Profits Protection Agency.

Just the facts — Nov 30 2015 10:23 PM

Luckily it's easy enough to just mix the two herbicides together. Until the EPA approves a commercial product, farmers will simply do just that, and probably at does higher than they really need.

This article is so absurd. Comparing this to an "arms race" as if the next herbicide is necessarily more powerful than the last is complete BS.

If there is a more natural solution that farmers will actually like, focus on that. If it exists, it will catch on. Meanwhile, quit trying to mislead people. The ends don't justify the means.

Comments are closed for this post.

Exhibit M

Citing Health Risks, Doctors And Scientists Urge Congress To Reject Potent Herbicide Mix For Genetically Engineered Crops

(202) 667-6982
ssciammacco@Ewg.org
FOR IMMEDIATE RELEASE: WEDNESDAY, JULY 23, 2014

Washington, D.C. – Prominent doctors, scientists and business leaders today urged Congress to pressure the Obama administration to reject an application to market "Enlist Duo™," a new toxic herbicide mix of 2,4-D and glyphosate.

The Environmental Protection Agency is currently reviewing an application from Dow AgroSciences, a wholly owned subsidiary of Dow Chemical Co., to sell Enlist Duo for use in agriculture. Enlist Duo would be used on millions of acres of farm fields in combination with a new type of herbicide-resistant, genetically engineered crops.

The medical and scientific experts told a Congressional briefing that this would put human and environmental health at risk.

The U.S. Department of Agriculture is weighing a separate application from Dow to market corn and soybean seeds that the company genetically engineered to tolerate the 2,4-D/glyphosate combination.

Those who spoke at the briefing to oppose Dow's application included Dr. Philip Landrigan of Mount Sinai School of Medicine, Dr. Catherine Thomasson of Physicians for Social Responsibility, John P. Wargo, Ph.D. of Yale University, Doug Gurian-Sherman, Ph.D. of Center for Food Safety and Gary Hirshberg of Stonyfield Farm and the advocacy group Just Label It.

Click here to listen to a full audio recording of the briefing.

"Exposures to herbicides in early life can lead to disease in childhood or disease later on in adult life or even old age," said Dr. Landrigan, dean for global health at Mount Sinai School of Medicine. "Herbicide chemicals can also cross from mother to child during pregnancy and prenatal exposures that occur during the nine months of pregnancy are especially dangerous."

"Physicians are very concerned about exposure to the combination of 2,4-D and glyphosate because of the potential lifelong and irreversible effects on the health of vulnerable populations, including children, pregnant women and farm workers," said Dr. Thomasson, executive director of Physicians for Social Responsibility. "Policy decisions should take into account the costs that can result from failure to act on the available data on toxic herbicides."

Americans are already exposed to 2,4-D in herbicides applied to lawns, turf grass and other non-agricultural sites. Exposure to the toxic defoliant has been linked to non-Hodgkin lymphoma and Parkinson's disease as well as immune system, thyroid and reproductive problems. Glyphosate is the harmful active ingredient in Roundup, the infamous weed killer developed by chemical giant Monsanto.

"2,4-D already is permitted by EPA to remain as residues on over 300 different forms of food," said John P. Wargo, Ph.D., professor of environmental health and politics at Yale University. "Spraying millions of additional acres with these chemicals will increase their contamination of soils, surface and groundwater and foods bearing their residues. If applied by aircraft, sprays will drift to adjacent lands, potentially endangering those who reside, go to school or work nearby."

Crops genetically engineered to withstand Roundup were introduced in the mid-90s. As scientists predicted, weeds quickly developed resistance to the herbicide, which in turn led to the use of hundreds of millions more pounds of the weed killer than would have occurred without these crops.

"The toxic herbicide mix is being proposed because glyphosate alone is no longer working, since its overuse has led to the development of herbicide-resistant 'superweeds'," said Gary Hirshberg, chairman of Stonyfield Farm and Just Label It. "This 'chemical treadmill' benefits the GE patent holders at the expense of farmers, human health and the environment."

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Blog Post: Chicago Tribune Exposé: EPA Cooked the Books to OK Dow's Dangerous Weed Killer

“The biotech industry is about to repeat the same mistakes that got us into this predicament,” said Doug Gurian Sherman, Ph.D, senior scientist with Center for Food Safety. “The public must demand policies and research that help farmers adopt proven, ecologically-based farming systems with minimal pesticide use that are productive, profitable and better for society.”

In June, 35 doctors, scientists and researchers, including Dr. Chensheng (Alex) Lu of Harvard School of Public Health and Dr. Raymond Richard Neutra, a retired division chief of the California Department of Public Health, sent a **letter** to EPA Administrator Gina McCarthy urging her to deny Dow’s application.

Before the public comment period ended, EPA received **half a million comments** opposing the controversial proposal.

“The risks of approving a new 2,4-D mixture are clear,” said Mary Ellen Kustin, senior policy analyst at the Environmental Working Group. “If approved, the use of 2,4-D would increase three-to-sevenfold by 2020, according to the USDA. The risks are too great and benefits too few to jeopardize public health and the environment.”

KEY ISSUES: TOXICS 2,4-D PESTICIDES FOOD CHEMICALS IN FOOD GMO FOODS

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Exhibit N

Opinion / Editorial

Editorial Escalating the weed wars

By **The Times Editorial Board · Contact Reporter**

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The way to deal with so-called superweeds isn't by escalating the arms race against them

SEPTEMBER 29, 2014, 5:32 PM

When crops were first introduced that had been engineered to withstand the herbicide glyphosate — better known by the trade name Roundup — the agricultural industry said it would confer a terrific environmental advantage. Glyphosate is a relatively benign herbicide, after all, and the industry claimed it would be able to use less of it to get rid of weeds, without harming the corn or soy.

At first, farmers did spray less glyphosate. But resistant versions of the weeds soon cropped up. That meant heavier, repeated spraying, which in turn meant more resistant weeds.

No problem, agribusiness said. We'll just make new crops genetically engineered to resist other herbicides.

But that's not a solution. Just as the nation must stop overusing antibiotics if it hopes to slow the emergence of resistant infections, it must do the same with herbicides and genetically modified crops. The way to deal with so-called superweeds isn't by escalating the arms race against them.

Article continues below ↓

A new generation of herbicide-resistant crops is wending its way through the federal approval process. A division of Dow Chemical recently won the approval of the U.S. Department of Agriculture for corn and soy that have been bioengineered to withstand spraying with both glyphosate and 2,4-D, a more toxic weed-killer that some critics say is dangerous to the environment and to people. Why both? About 18 weeds have developed resistance to 2,4-D over the more than 50 years it has been in use. So the idea is to use both herbicides, with each one eradicating the weeds that the other one can't.

But first, the Environmental Protection Agency would have to approve the special blending of the two herbicides developed by Dow. Called Enlist Duo, the mix has been formulated not to drift over large areas as 2,4-D commonly does. It would thus reduce the risk of killing crops miles away. According to USDA estimates, the introduction of the new crops would mean the spraying of five to 13 times as

much 2,4-D by the year 2020.

Meanwhile, Monsanto, the developer of Roundup Ready corn, is developing its own new generation of herbicide-resistant crops able to withstand a third weed killer.

The USDA considers only whether the genetically engineered seeds represent a hazard to other crops; the EPA is responsible for overseeing the safety of herbicides used in agriculture. No agency looks at the bigger policy question of whether the nation is embarking on a potentially dangerous path toward creating ever-more-resistant weeds and spraying them and crops with larger and larger doses of stronger herbicides. That question should be answered before the country escalates the war out in the fields.

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Exhibit O

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: October 14, 2014
Subject: Response to Public Comments Received Regarding New Uses of Enlist Duo™ on Corn and Soybeans
Product Name: Enlist Duo™
EPA Registration Number: 62719-649
Application Date: November 1, 2011

Response to Comments

The Agency received 417,301 comments in response to the public participation process (Docket ID: EPA-HQ-OPP-2014-0195) regarding the Environmental Protection Agency's (EPA's) proposed decision for the application to register the use of 2,4-D choline salt on (Genetically Engineered) GE 2,4-D and glyphosate tolerant corn and soybeans. Comments received were both in favor of and opposed to the decision to register Enlist Duo™, which will provide growers with additional tools to control a broad spectrum of weeds. The EPA welcomes input from the public during the decision process when registering pesticides, and is committed to thoroughly evaluating and mitigating any potential risks from registered pesticides, consistent with applicable statutory standards. Also, EPA strives to document and explain the basis of its regulatory decisions through these and other public documents.

I. Human health

A common concern expressed in the submitted comments regarded the human health effects of the potential increased use, and therefore exposure of, 2,4-D. Because similar human health issues were raised by many commenters, the comments are grouped into major topic areas and each topic area is addressed below. These topic areas fall under 4 major headings: toxicity, risk, exposure, and epidemiology/incidents.

A. Toxicity

Commenters questioned EPA's assessment of toxic effects including developmental, mutagenic, thyroid, endocrine, cancer, reproductive, immunotoxic, and kidney effects. Commenter's questions focused on how a safety finding could be made when these effects were observed in some toxicity studies, and they expressed concerns about the completeness and adequacy of the toxicity database. In order to address these comments, EPA first presents two important overarching considerations; second, we discuss the Agency's consideration of

the toxic effects regarding each organ system. Following this discussion, EPA identifies and responds to other specific comments regarding toxicity.

1. Overarching Considerations

First, the toxicity database for 2,4-D is complete and robust. This includes a recently completed and reviewed Extended One-Generation Reproductive Toxicity Study (EOGRTS), a study which measures numerous toxic effects in multiple organ systems (endocrine, thyroid, reproductive, developmental, immuno-, and nervous), and across the lifetime of an organism from conception to adulthood. EPA also completed a thorough literature search considering all pertinent toxicity research and found no information which would change the conclusions drawn in the Agency's risk assessment.

A second overarching consideration in responding to commenters' questions is the pharmacokinetic behavior of 2,4-D. 2,4-D is readily absorbed into the blood stream, is removed from the blood by the kidneys unchanged (it is not metabolized), and is rapidly excreted *via* the urine. At high dose levels, renal saturation occurs, which means that the ability of the kidney (renal) to excrete 2,4-D is overwhelmed. As a consequence, 2,4-D builds up in the body. When this occurs, toxic effects are observed. Studies referenced by some commenters utilized dose levels above those causing renal saturation. **However, at doses below those causing renal saturation, toxic effects are not observed.** This is an essential consideration in EPA's 2,4-D assessment: the Agency's assessment establishes a maximum allowable dose which is at least 100-fold below this level, assuring protection of public health, and the levels at which people might be exposed are far below even this level since estimated risks are well below the maximum allowable exposure threshold. Therefore, the Agency's assessment is protective for any effects seen in these studies.

2. Agency Consideration of Toxic Effects regarding Each Organ System

a. Developmental Effects

2,4-D has been thoroughly studied with respect to potential effects on the developing animal. There are two (rat and rabbit) guideline developmental toxicity studies on 2,4-D, which are designed to provide information concerning the effects of exposure of the pregnant test animal on the developing organism (fetal effects including death, structural abnormalities, or altered growth) and an assessment of maternal effects. Functional deficiencies and other postnatal effects have been assessed in the guideline 2-generation reproduction study on 2,4-D and in the 2,4-D extended 1-generation reproduction study, which included a developmental neurotoxicity and immunotoxicity assessment. Developmental toxicity was identified/observed in the rat and rabbit developmental toxicity studies at a maternally toxic dose that exceeded the maternal animal's ability to excrete 2,4-D (i.e., above levels of renal saturation; see *2,4-D. Human Health Risk Assessment for a Proposed Use of 2,4-D Choline on Herbicide-Tolerant Corn and Soybean*, LaMay, August 8, 2013). There are clear no-observed-adverse-effect levels (NOAELs; defined as doses at which no adverse toxic effects are

seen in toxicology studies, and upon which the Agency's estimates are typically quantified) in both studies for the developmental effects observed, and an acute dietary risk assessment point of departure (POD; defined as the NOAEL or other dose level to which safety factors are typically applied when quantifying risks) is based on the rat developmental toxicity study [where fetal skeletal abnormalities (14^{th} rudimentary ribs were observed at a dose level that exceeded the maternal animal's ability to excrete 2,4-D)]. Therefore, the Agency has considered and addressed concerns for developmental toxicity in its risk assessment.

b. Mutagenicity

While the concern for mutagenicity was raised by commenters, no supporting evidence was provided. Similar claims were submitted by the Natural Resources Defense Council (NRDC) in a November 6, 2008 petition requesting that EPA revoke all pesticide tolerances for 2,4-D under section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), and were thoroughly addressed by the Agency in an April 18, 2012 Order denying that petition (*see* 77 FR 23135, 23149-23151 (Apr. 18, 2012)). EPA's current testing requirements focus on tests for mutagenic effects, *i.e.,* heritable changes in DNA that could potentially lead to disease. Based on a full battery of mutagenicity testing, 2,4-D is not considered to be a mutagen.

c. Thyroid Toxicity

The Agency identified thyroid toxicity as a potential effect of concern and required additional testing. Potential for thyroid toxicity was assessed in the extended one-generation reproduction study (EOGRTS) on 2,4-D, which assessed numerous thyroid parameters. These included thyroid weights, thyroid hormone levels (T3, T4, TSH), and histopathology evaluation of the thyroid. These parameters were assessed in the young animal on postnatal days 4, 22, and 70 and in pregnant females on gestation day 17. At the highest dose tested, the predicted pattern of thyroid hormone changes that could signify a thyroid effect was observed in the adult females (*i.e.,* ↓T3 and ↓T4 with ↑TSH levels). These hormone findings are considered treatment-related but adaptive and not adverse; i.e., the thyroid responded to the insult and corrected itself. The thyroid findings in the other age groups were not treatment-related because there was no dose-response in the changes, and/or the predicted pattern of thyroid hormone changes was not evident. In this study and in other studies where thyroid effects were observed, clear NOAELs were identified, and the endpoints selected for risk assessment are protective of potential thyroid effects. EPA has quantified risk of 2,4-D to assure exposures are at least 100-fold lower than levels where renal saturation occurs.

d. Endocrine Effects

The Agency has comprehensively evaluated the endocrine effects of 2,4-D. As noted in the Order denying the NRDC petition seeking revocation of 2,4-D tolerances under the FFDCA (77 FR 23135 (Apr. 18, 2012)), potential hormonal effects can be detected

through behavioral changes, ability to become pregnant, duration of gestation, signs of difficult or prolonged parturition, apparent sex ratio (ascertained by anogenital distances of the offspring), feminization or masculinization of offspring, number of pups, stillbirths, gross pathology and histopathology of the vagina, uterus, ovaries, testis, epididymis, seminal vesicles, prostate, and any other identified target organs. EPA concluded in its review of the data submitted as part of this petition that the rat two-generation reproduction study protocol described in the 1998 test guidelines is valid for the identification and characterization of reproductive and developmental effects, including those due to endocrine disruption, based on the long history of its use, the endorsement of the 1998 test guideline by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP), and acceptance by member countries of the Organisation for Economic Cooperation and Development (OECD). The results of this study were consistent with other toxicity studies in the database showing that toxic effects occur only at doses above levels of renal saturation.

In addition to the 1998 test guideline for the mammalian two-generation reproductive toxicity study, EPA has proposed the new OECD test guideline for the extended one-generation reproductive toxicity study (EOGRTS) as an alternate EDSP (Endocrine Disruptor Screening Program) Tier 2 test. The extended one-generation reproductive toxicity study was not only designed to provide the traditional spectrum of information from a reproductive study, but was also enhanced to evaluate reproductive and developmental endpoints associated with the endocrine, nervous, and immune systems in male and female adult rodents and offspring at birth, weaning, and puberty, which may not necessarily be covered in other 40 CFR part 158 test guideline studies.

Both the rat two-generation reproduction study and the EOGRTS are available for 2,4-D and have been evaluated by the Agency and incorporated into the hazard assessment of 2,4-D.

The EOGRT study on 2,4-D examined endocrine related parameters, which included parental (male and female) reproductive function; offspring survival, growth, and development; endocrine and systemic toxicity parameters, including estrous cyclicity (adult and offspring); sperm parameters; anogenital distance; nipple retention; sexual maturation (vaginal opening and balano-preputial separation); organ weights (adrenal, thyroid/parathyroid, pituitary, testes and ovaries/other reproductive organs, liver, kidney); thyroid hormone effects; and histopathology of the thyroid, adrenal, pituitary, liver, pancreas, testes, and ovary/other reproductive organs. For all of the parameters assessed, a clear NOAEL (= 21 mg/kg/day) was identified, which was used as the point of departure for risk quantification, and as in other toxicity studies in the database, adverse toxic effects were observed only at levels that exceed the body's ability to excrete 2,4-D.

Finally, in response to the 2009 Test Order, EPA determined not to require the *in vivo* mammalian Tier 1 tests for 2,4-D (i.e, Uterotrophic, Hershberger, the Male and Female Pubertal Assays) due to the availability of the extended one generation reproduction

study. EPA has received all required final study reports and data for the five *in vitro* assays from the Tier 1 battery for 2,4-D. Although the submitted Tier 1 *in vitro* studies may inform EPA on mechanistic issues in mammalian systems (e.g., whether 2,4-D can bind to the estrogen or androgen receptor in mammals), the studies will not affect EPA's conclusions on the quantitative endocrine risks posed by 2,4-D for humans given the availability of the extended one-generation reproduction study that comprehensively examined the risks to human health from 2,4-D's interaction with endocrine system endpoints.

e. Cancer

Studies in rats and mice showed no statistically significant tumor response in either species; furthermore, 2,4-D is not mutagenic, a flag for potential carcinogenicity. The Agency determined, based on several reviews of epidemiological studies, in addition to the animal studies, that the existing data did not support a conclusion that links human cancer to 2,4-D exposure. This is further discussed in the Agency's response to epidemiology comments. In accordance with the Agency's 1986 "Guidelines for Carcinogen Risk Assessment, 2,4-D was classified a "Group D Chemical: Not Classifiable as to Human Carcinogenicity." This classification was based on the lack of evidence of carcinogenicity in two well-designed and well-conducted animal studies of adequate power and dose in two species (mice and rats), and on the lack of epidemiological data supporting an association between 2,4-D exposure and cancer. Although 2,4-D's classification has not be been evaluated according to the 2005 classification scheme, based on weight of evidence consideration of the available data, 2,4-D would be classified as "Not Likely to be Carcinogenic to Humans."

f. Reproductive Effects

For 2,4-D, there are two studies that specifically assess reproductive toxicity. These are the 2-generation reproduction toxicity study and the extended one-generation reproductive toxicity (EOGRT) study. Evidence of possible reproductive effects observed in the 2,4-D database at dose levels that exceeded the rat's ability to excrete 2,4-D led to the requirement of further testing included in the EOGRTS. In the EOGRT study, the following reproductive parameters were assessed: parental male and female reproductive function; offspring growth and development; estrous cyclicity (adult and offspring); sperm parameters; anogenital distance; nipple retention; sexual maturation (vaginal opening and balano-preputial separation); organ weights (testes and ovaries/other reproductive organs); and histopathology (testes, ovary, and other reproductive organs). For all of the parameters assessed, a No-Observed-Adverse-Effect Level (NOAEL) was identified and selected as the point of departure for risk assessment. Since there were no adverse effects observed at this dose, quantifying risks using this dose is protective for any effects occurring at higher dose levels that exceed the body's ability to excrete 2,4-D.

Commenters expressed specific concerns regarding certain reproductive effects. These include estrous cycle changes, increased uterine weights, and effects on male reproductive organ weights. Estrous cycle changes observed were not an adverse effect; differences in the stage of cycling are normal among females. An adverse effect would be the lack of cycling or persistent estrous, which did not occur. Regarding increased uterine weights, the pattern of effects must be considered when determining whether the effects are adverse. For 2,4-D there was no consistent pattern of perturbations in the estrogen pathway as evidenced by the lack of effects in a number of estrogen-dependent parameters including but not limited to pregnancy rate, number corpora lutea, estrous cycling, and sexual maturation. Given that none of these were affected, an isolated finding of increase in uterine weights is not considered adverse. Finally, regarding male reproductive organ weight effects, a pattern of effects is again important when considering whether the effect is adverse. In this case there was no consistent pattern of androgenicity observed, fertility was not affected, mating behavior was normal, sexual maturation was not affected, and sperm motility, count and morphology were unaffected. Therefore, the effect was not considered adverse.

Also, see the response above for endocrine effects for additional information.

g. Immunotoxicity

The standard suite of immunotoxicity effects were measured in the EOGRTS. One measure of the *potential for* immunotoxicity is thymus effects, and decreased thymus weight was observed in the EOGRTS. However, changes in thymus weight alone are not an indication of immunotoxicity. The decreases observed in thymus weight in the EOGRT study showed no dose-response, and there were no histopathological changes in the thymus. Moreover, no evidence of a functional deficit in the immune system was observed in the SRBC AFC (Sheep Red Blood Cell Antibody Forming Cell) response and the Natural Killer Cell Activity assays at dose levels approaching or exceeding renal saturation. In the absence of these additional findings, the decreased thymus weight is not considered an effect of concern.

h. Kidney Effects

The kidney is the major target organ of 2,4-D. 2,4-D is readily absorbed into the blood, removed from the blood by the kidneys unchanged, and excreted *via* the urine. At dose levels in the rat greater than 50 mg/kg/day, the ability of the kidney to excrete 2,4-D is overwhelmed, and 2,4-D builds up in the body resulting in toxic effects. For all of the kidney parameters assessed in the studies on 2,4-D, clear No-Observed-Adverse-Effect Levels (NOAELs) were identified. Points of departure selected for quantifying risk assessment are below levels at which kidney effects were observed and are therefore protective of any potential kidney effects occurring at higher dose levels that exceed the body's ability to excrete 2,4-D.

3. Responses to Other Specific Comments Regarding Toxicity

Comment: *Synergistic effects of 2,4-D and glyphosate and/or formulation inerts must be considered*

Response: The Agency routinely requires submission of acute toxicity data for both individual pesticide active ingredients and formulated pesticide products. Acute oral, dermal, and inhalation data, skin and eye irritation data, and skin sensitization data are available for the 2,4-D choline salt and glyphosate formulation for comparison with the 2,4-D parent compound and glyphosate parent compound data, and these test results show similar profiles. The mixture does not show a greater toxicity compared to either parent compound alone. Although no longer duration toxicity studies are available, toxic effects would not be expected as the maximum allowed 2,4-D exposure is at least 100-fold below levels where toxicity to individual chemicals might occur, and exposure to people is far below even that level.

Comment: *Toxicity of the 2,4-D metabolite, 2,4-dichlorophenol (2,4-DCP), must be considered*

Response: There are adequate toxicity data available on 2,4-DCP, which show that 2,4-DCP is less toxic than 2,4-D (i.e., higher dose levels are tolerated; NOAELs/LOAELs are higher). Both the rat National Toxicology Program (NTP) carcinogenicity and mouse NTP carcinogenicity studies (1989) on 2,4-DCP are negative for carcinogenicity. In the 2-generation reproduction study on 2,4-DCP, the NOAEL for effects on offspring is 2,000 ppm (134 mg/kg/day), based on a slight decrease in the number of pups, delayed eye opening in both sexes and generations, and slight (≤1 day) delays in sexual maturation at 543 mg/kg/day. The reproductive toxicity NOAEL is 2,000 ppm (134 mg/kg/day, based on decreased number of implantation sites (F1 parental/F2 offspring) at the LOAEL of 543 mg/kg/day. Developmental toxicity was not observed in the rat.

Although 2,4-DCP is shown to be less toxic than 2,4-D, the Agency assessment assumes 2,4-DCP is as toxic as 2,4-D – thus the risk assessment over-estimates risk and could be refined by considering the reduced toxicity of the metabolite. However, this is not necessary since the assessment assuming equivalent toxicity showed no risks of concern.

Comment: *EPA should use the 2,4-D dose of 100 ppm, not 300 ppm, as the point of departure for human health risk assessment and apply an additional 10-fold safety factor to protect children's health, pursuant to the Food Quality Protection Act.*

Response: The commenter indicated that toxic effects were observed in the EOGRTS below 300 ppm, the dose selected by the Agency as the No Observed Adverse Effect Level (NOAEL). The effects included increased uterine weight, decreased reproductive organ weight in males, thyroid hormone level changes, decreased thymus weight, and kidney effects. Each of these was discussed earlier, but are repeated below to provide in one place a concise response to specific concerns raised regarding the EOGRTS.

Regarding the reproductive effects, the Agency's conclusions were based on the following. Differences in the stage of estrous cycling are normal among females; an adverse effect would be the lack of cycling or persistent estrous, which did not occur in the study. Increased uterine weight was not considered adverse since there was no consistent pattern of estrogenicity, pregnancy rate was not affected, the number corpora lutea was unaffected, estrous cycling was normal, and sexual maturation was not affected. Regarding male reproductive organ weight effects, there was no consistent pattern of androgenicity observed, fertility was not affected, mating behavior was normal, and sexual maturation was not affected.

Regarding thyroid toxicity, at the highest dose tested, the predicted pattern of thyroid hormone changes that could signify a thyroid effect was observed in the adult females (*i.e.,* ↓T3 and ↓T4 with ↑TSH levels). These hormone findings are considered treatment-related but adaptive and not adverse; i.e., the thyroid responded to the insult and corrected itself. The thyroid findings in the other age groups were not treatment-related because there was no dose-response in the changes, and/or the predicted pattern of thyroid hormone changes was not evident.

The standard suite of immunotoxicity effects were measured in the EOGRTS. One measure of the *potential for* immunotoxicity is thymus effects, and decreased thymus weight was observed in the EOGRTS. However, changes in thymus weight alone are not an indication of immunotoxicity. The decreases observed in thymus weight in the EOGRT study showed no dose-response, and there were no histopathological changes in the thymus. In the absence of these additional findings, the decreased thymus weight is not considered an effect of concern.

For all of the kidney parameters assessed in the studies on 2,4-D, clear No-Observed-Adverse-Effect Levels (NOAELs) were identified, and the points of departure selected for risk assessment are protective of any potential kidney effects occurring at dose levels that exceed the body's ability to excrete 2,4-D.

The conclusions drawn by the Agency regarding setting of NOAELs and LOAELs for the EOGRTS are consistent with accepted standards for evaluation of toxicology data and determination of whether a toxic effect should or should not be considered adverse. Comments regarding EPA's decision to reduce the FQPA safety factor to 1X are addressed below.

Although the Agency believes its decision to establish the NOAEL from the EOGRTS at 300 ppm and to reduce the FQPA safety factor to 1X is scientifically sound and consistent with established science policy, in order to more fully characterize risk potential, risks were also assessed using the NOAEL = 100 ppm as the risk assessment point of departure and retaining the FQPA safety factor of 10X. Using these inputs, risks were still acceptable for all age groups for all components of the assessment: dietary food and drinking water exposure, volatility, spray drift, residential, and aggregate assessment.

Comment: *The Agency's assessment was largely based on forms of 2,4-D other than the choline salt; the choline salt may exhibit differences in toxicity and absorption relative to other forms of 2,4-D*

Response: The extensive database on 2,4-D was used in the risk assessment on the choline salt of 2,4-D. This is consistent with the use of the 2,4-D database for other 2,4-D salts. There are data that demonstrate similar toxicities among the various salts of 2,4-D, and there are data available to show that 2,4-D salts readily dissociate into 2,4-D acid and the cation. The counter-ion in the Enlist Duo™ formulation, choline, is an essential nutrient, and not of toxicological concern.

Commenters provided no data to substantiate or explain the concern for differences in absorption. As noted above, choline is an essential nutrient, and available toxicity data demonstrate a similar toxicology profile across 2,4-D salts. A similar toxicity profile suggests that any differences in absorption are not of concern.

B. Risk

Comment: *The Food Quality Protection Act (FQPA) "additional tenfold margin of safety" to protect infants and children should be applied because the Agency's toxicity and exposure assessments do not adequately protect childrens' health*

Response: As a result of Section 405 of the Food Quality Protection Act of 1996 (P.L. 104-170), in establishing a "tolerance" under section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), section 408(b)(2)(C) of the FFDCA states, in part, that:

> "… an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

This is commonly referred to as the "FQPA safety factor" or the "10X" safety factor.

Section 2(bb) of FIFRA, in turn, defines "unreasonable adverse effects on the environment" to mean, in part: "… a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under section 408 of the [FFDCA]."

Whether a margin of safety different from the tenfold margin of safety under this provision should be applied was assessed in a manner consistent with all pesticide assessments. Major considerations include the completeness of the 2,4-D database with respect to toxicity and exposure, whether the assessment is protective for any observed sensitivity in infants and

children (including developing fetuses), and whether the exposure data is protective for exposure to infants and children (including fetuses).

As discussed in other comment responses, the Agency has a complete and robust database for 2,4-D for both toxicity and exposure. Please refer to other specific comments for details.

Increased sensitivity was observed in fetuses in the rat developmental study and the rat 2-generation reproduction study. In order to assure that the human health assessment adequately protected children and fetuses for these sensitivities, doses were chosen for regulation which were below the levels at which these effects were seen, i.e., the starting points for determining maximum allowable human exposures (before applying any safety factors) were well below levels at which these more sensitive toxic effects were observed – this assures protection of infants and children for these sensitivities. Additional safety factors of 10X for extrapolation across species and 10X for variability within the human population (total = 100X) were then applied to these doses to assure adequate human health protection.

The Agency assessed all potential 2,4-D exposure pathways for children for all uses of the chemical – dietary exposure through food and drinking water, residential exposures, spray drift, volatilization, and swimming – using protective assumptions which will not underestimate childrens' exposures. These exposure assessments are discussed in detail in the exposure section of this response (pp. 12-17).

Based on these 3 considerations – a complete database for toxicity and exposure, adequate protection for sensitivity in infants and children, and an exposure assessment which will not underestimate childrens' exposures – sufficient reliable information is available showing that risks to infants and children will not be underestimated, and EPA determined that the 10X FQPA safety factor could be reduced to 1X, consistent with the requirements of the Food Quality Protection Act.

Comment: *EPA failed to thoroughly examine all of the significant health and environmental risks of 2,4-D including that of inhalation and aggregate exposure*

Response: EPA thoroughly examined all of the significant environmental and health risks of 2,4-D including inhalation and aggregate exposure. EPA's inhalation assessment evaluated risks using the most sensitive toxic effect – effects in the respiratory tract. Exposure to both residential pesticide users and professional applicators who would be applying the new 2,4-D formulation to herbicide resistant corn and soybeans were well below levels of risk concern.

Regarding inclusion of inhalation exposure in the aggregate assessment, aggregating exposures when toxic effects are different for the different exposure routes (e.g., oral and inhalation) is not scientifically appropriate. Furthermore, EPA calculated the systemic dose corresponding to the inhalation level at which the very sensitive portal of entry inhalation effects occur. These Human Equivalent Doses (HEDs) are well below levels at which effects from oral exposure are regulated; therefore, regulating based on the portal of entry effects will be protective for any contribution from inhalation route to the aggregate exposure.

EPA's aggregate exposure assessment included contributions from food, drinking water, and non-occupational exposure, and was done for both adults and children. High-end, unrefined screening level inputs were used which resulted in exposure estimates well below levels of risk concern. Adult aggregate exposure included contributions from food, drinking water, and incidental oral exposure from swimming in a 2,4-D treated water body; the aggregate MOE was 1,800. Children's aggregate exposure included contributions from food, drinking water, and incidental oral exposure hand to mouth from turf; the aggregate MOE was 340.

Therefore, EPA's risk assessment considered both inhalation and aggregate exposures and concluded that there were no risks of concern.

Comment: *2,4-D is a major source of dioxins presenting risk concerns for use of the chemical; 2,4-D is a component of Agent Orange and therefore of significant risk concern*

Response: As a result of changes in the manufacturing processes for 2,4-D over the past 15-20 years, dioxins are no longer found at detectable levels in 2,4-D products sold and used in the United States. The Agency has required testing of all 2,4-D products for dioxins using very sensitive methods. Additionally, the Agency conducted an assessment assuming that dioxins were present at the detection limit in all 2,4-D products – an implausible situation, but a very protective assumption. Human health risks assessed with this assumption were insignificant.

Related to the dioxin comments, some commenters questioned 2,4-D's hazard potential referring to its presence in Agent Orange, a defoliant used during the Vietnam War thought to cause a range of health effects. Although 2,4-D is known as one of the components of Agent Orange, it is not the one responsible for the adverse health effects experienced by those exposed to Agent Orange. Agent Orange was a mixture of two different herbicides—2,4,5-T and 2,4-D—as well as kerosene and diesel fuel. Agent Orange contained high levels of dioxin, a contaminant found in 2,4,5-T that causes cancer and other health concerns in people. EPA cancelled all use of 2,4,5-T in 1985 because of these risks.

Comment: *EPA must consider cumulative risk to 2,4-D and other structurally related compounds*

Response: Chemicals from the same chemical class have been identified and will be further investigated as a possible common mechanism group during the Agency's Registration Review process. However, we note that the compounds with the closest structural similarity to 2,4-D are 2,4-DB (4-(2,4-dichlorophenoxy)butyric acid) and 2,4-DP (2-(2,4-dichlorophenoxy)propanoic acid). The most recent assessments indicate that the dietary risks for these compounds are insignificant. Furthermore, using a highly protective screening-level approach of combining high-end children's risks from the two chemicals results in no risks of concern.

Comment: *2,4-D is linked to Non-Hodgkin's Lymphoma (NHL)*

Response: The FIFRA Scientific Advisory Panel, a Federal Advisory Committee with whom EPA consults regarding novel or contentious scientific issues, evaluated the cause and effect relationship between exposure to 2,4-D and non-Hodgkin's lymphoma in 1994. They concluded that "*data are not sufficient to conclude that there is a cause and effect relationship between exposure to 2,4-D and non-Hodgkin's lymphoma,*" and "*[s]ome case-control studies have shown a risk of non-Hodgkin's lymphoma (NHL) in association with farming but many of these studies did not control for other agents in addition to 2,4-D.*" (US EPA, March, 1994. AN SAB REPORT: ASSESSMENT OF POTENTIAL 2,4-D CARCINOGENICITY. REVIEW OF THE EPIDEMIOLOGICAL AND OTHER DATA ON POTENTIAL CARCINOGENICITY OF 2,4-D BY THE SAB/SAP JOINT COMMITTEE)

In both 1996 and 2004 further reviews were conducted of additional epidemiological studies by Blondell (D311464, 12/8/04) both with similar conclusions.
In 2012, the Agency considered additional information provided by the Natural Resources Defense Council regarding, among other things, 2,4-D's linkage to non-Hodgkin's lymphoma, again resulting in similar conclusions.

Most recently, an abstract was presented at the 23rd Conference on Epidemiology in Occupational Health (EPICOH 2.0.13; Improving the Impact, 18-21 June, 2013, the Netherlands, Freeman, et. al.) considering a prospective cohort of licensed pesticide applicators within the National Agricultural Health Study. The results of this study showed no association between 2,4-D and non-Hodgkins lymphoma.

While there has been much focus on epidemiology data suggesting a linkage between NHL and farm work, there is insufficient scientific evidence supporting a specific linkage with 2,4-D. Furthermore, this linkage is not supported by data on laboratory animals as discussed in the cancer assessment portion of this response.

Based on the available epidemiology data and controlled studies, the Agency therefore concludes that there is not sufficient information to show a cause and effect linkage between 2,4-D exposure and NHL. This conclusion was also reached by Health Canada's Pesticide Management Regulatory Agency.

Comment: *2,4-D is linked to Parkinson's disease (PD)*

Response: The Agency has reviewed key literature regarding the link between 2,4-D exposure and Parkinson's Disease, including the recent epidemiology report sponsored by the European Food Safety Authority (EFSA). Overall, six key studies explicitly evaluated the putative association of PD with 2,4-D exposure, with four studies documenting elevated risks (Odds Ratios (OR) >1) and two studies finding no increased risk. Of the four studies associating elevated odds for PD with 2,4-D exposure, only one study had statistically significant results (Tanner et al., 2009). Although Tanner et al. (2009) did find a significant association between 2,4-D exposure and PD with OR of 2.59 (95% CI= 1.03, 6.48; *p*-value= 0.04), they did not find a statistically significant evaluated risk associated with 2,4-D in 2011

(OR of 1.2 for men and women, with the CI, 0.57-2.4). Overall, the Agency concludes that the available evidence is not sufficient to conclude that there is a causal link between exposure to 2,4-D and PD.

C. Exposure

Comment: The *dietary risk assessment does not adequately capture all reasonable exposure risks (assumptions were not adequately articulated; it was not clearly demonstrated that breast milk was considered in dietary exposure assessment; high levels of 2,4-D metabolites were not adequately considered; must incorporate increased use of 2,4-D into the assessment)*

Response: Field trials were conducted in which 2,4-D tolerant corn and soybean were treated with 2,4-D choline according to label directions, and in the manner likely to lead to highest potential food residues. These field trials were used to determine the residue levels of 2,4-D and 2,4-DCP (2,4-dichlorophenol) in tolerant corn and soybean, which were used in the updated dietary risk assessment and for tolerance setting purposes.

For 2,4-D-tolerant field corn and soybean, the metabolite 2,4-DCP was included as a residue of concern for dietary risk assessment purposes, as there are greater amounts of 2,4-DCP found in resistant crop compared to non-resistant crop. Therefore, the dietary assessment considered the combined residues of 2,4-D and 2,4-DCP in tolerant corn and soybean based on use patterns expected to result in the highest food residues (maximum use rates, maximum number of applications, minimum interval between applications, minimum interval between last treatment and harvest). Furthermore, the Agency assumed tolerance level residues (or higher) in all crops – the tolerance is a statistically-derived upper bound on allowable residues in crops which will not be exceeded with legal use of the pesticide.

Additionally, the dietary risk assessment assumed that 100% of the U.S. corn and soybean crops are treated to account for potential increased use of 2,4-D.

Livestock can also ingest 2,4-D and its metabolites in their diets as a result of eating treated feeds such as corn grain. The Agency's assessment of residues in meat, milk, poultry and eggs will not change as a result of increased usage on any given feed item since the percentage of crop treated is not factored into these assessments; the entire feed crop is assumed to be treated, and livestock are assumed to ingest the corresponding residues. Therefore, the high-end residues and dietary risk estimates assumed to potentially result in livestock commodities will not increase if the usage of 2,4-D expands.

In assessing 2,4-D exposure from breast milk consumption, the Agency considered available data on the ruminant metabolism and magnitude of the residue; a tolerance for residues of 2,4-D in cow's milk is set at 0.05 ppm. As stated above, the tolerance is a statistically-derived upper bound on allowable residues which will not be exceeded with legal use of the pesticide.

The Agency also considered the chemical properties of 2,4-D, specifically the octanol-water partition coefficient (K_{OW}). This is one predictor of the potential for a pesticide or any

chemical to bioaccumulate because high values of K_{OW} indicate a tendency for a chemical to partition into lipids (fat, including milk fat) rather than water. Chemicals that partition into lipids can accumulate in the fatty tissues and milk of an organism, while chemicals that partition into water will be excreted rapidly. 2,4-D has a low log K_{OW} (log K_{OW} = 0.18 at neutral pH). This low value indicates that the chemical prefers to partition into water and would not partition into and accumulate in milk, fat and tissues. The metabolism study in rats confirms this showing that 2,4-D is well absorbed orally, undergoes limited metabolism, and is eliminated quickly from the body primarily unchanged in the urine by active saturable renal transport. Based on this information, EPA does not anticipate that residues in breast milk would be greater than those found in cow's milk. Since tolerance level residues in milk were used in the dietary risk assessment, the human health risk assessment is expected to be protective for breast milk consumption. No data have been submitted, or have been found by the Agency in the literature, refuting this conclusion.

Drinking water estimates used in the dietary assessment were derived from modeling using modeling inputs designed not to underestimate residues in drinking water. Modeled residue estimates are far higher than residues found in monitoring data. These residue estimates will not underestimate exposures to anyone in the U.S. population, and will be far higher than those to which the vast majority of the population will be exposed. Drinking water model descriptions are available on the EPA websites, and the models themselves are available for download. Specific inputs for the 2,4-D assessment are described in the Agency review of this action.

Finally, as discussed in the response to comments section on toxicity, the toxicity endpoint used in the dietary assessment for both 2,4-D and 2,4-DCP was for 2,4-D parent toxicity; since 2,4-DCP is less toxic than 2,4-D, comparing 2,4-DCP residues to 2,4-D endpoints is very protective.

In summary, using the highly protective assumptions described above, the acute and chronic dietary risk estimates for 2,4-D were not of concern for adults, children, pregnant women, or any other population group. Since the Agency assumed that all crops/foods with registered uses for 2,4-D would be treated, and that everyone who ate these foods would consume high-end residues of 2,4-D in all of these foods, any increased usage of 2,4-D will not result in risk estimates higher than those already calculated, which are not of concern.

Comment: *The Agency did not properly account for volatility of 2,4-D (did not consider available monitoring data; it's unclear if reasonable worst-case assumptions were used in the assessment; surfactants and solvents can alter 2,4-D volatility; temperature and field conditions can alter 2,4-D volatility; not enough information was provided on the 2,4-D flux data)*

Response: The Agency conducted a volatility assessment using health-protective assumptions.

2,4-D specific flux monitoring data were used for the volatility assessment. Trials were conducted at different sites (Indiana, Arkansas, and Georgia) to reflect a range of temperature

and field conditions. Trials were conducted with applications to bare soil, soybean (30 cm crop height with 80% canopy closure), soybean (15 cm crop height with 15% canopy cover), and cotton (50 cm crop height with 40% canopy cover). These flux studies used products with differing formulations: 2,4-D choline-specific flux study was completed using the experimental formulations (both 2,4-D choline alone and 2,4-D choline plus glyphosate end use products).

Results showed that 2,4-D choline salt has lower volatility than 2,4-D esters and other salts. The maximum application rate was used for the assessment.

Volatilization modeling was completed by the Agency using Probabilistic Exposure and Risk model for fumigants (PERFUM). Approaches EPA has used previously to assess inhalation exposures to fumigant pesticides were used for the assessment, consistent with the recommendations of the December 2009 Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) meeting on the scientific issues associated with field volatilization of conversional (semi-volatile) pesticides. The PERFUM modelling results are based on Bradenton, FL; Yakima, WA; Flint, MI; and Ventura, CA weather datasets which have been used in the past for other volatilization analyses and represent a range of conditions including those which have consistently provided the highest risk estimates.

The portal-of-entry inhalation toxicity endpoint was used in the volatilization assessment, the most sensitive inhalation toxicity observed for 2,4-D. By using this endpoint, the Agency assumed that bystanders are exposed every day for 28 consecutive days at the maximum, day-of-application volatilization exposure near the field – this is a very health-protective assumption. Combining this protective assumption with the exposure assumptions discussed above which reflect the highest exposure scenario results in a very health protective assessment.

Estimated risks from volatility will not increase if there is increased use of 2,4-D; the current assessment assumes that bystanders are exposed to air concentrations at the edge of a field treated using the use pattern likely to result in the highest residues possible.

Based on these assumptions, airborne concentrations of 2,4-D at the edge of the treated field are not of concern. Although the Agency believes its decision to reduce the FQPA safety factor to 1X is scientifically sound and consistent with established science policy, in order to more fully characterize risk potential, volatility risks were also assessed retaining the FQPA 10X safety factor. It should be noted that even with application of an additional 10X FQPA safety factor, there are no risks of concern at the field edge.

Comment: *Invalid assumptions were used for spray drift (an increased frequency of applications will cause increase in exposure; OPP should evaluate the AgDRIFT and AgDISP models according to CREM recommendations)*

Response: In assessing risks from spray drift, the Agency assumes that spray drifts onto a lawn adjacent to an agricultural field being treated, and children immediately play on that

lawn. This approach has been vetted both through the FIFRA Scientific Advisory Panel and a public comment process. If the pesticide being assessed also has a lawn use, and that lawn use has higher lawn turf residues than those estimated from spray drift, then risks from spray drift will be less than risks from lawn use - if the lawn use shows no risk concern, spray drift will have no risk concern. This is the case for 2,4-D.

The use rate for direct application of 2,4-D to residential turf exceeds the use rate on corn and soybean, thus the residential turf assessment is protective of any potential drift onto nearby lawns. The residential turf uses were assessed using the 2012 Residential Standard Operating Procedures as well as chemical-specific residue data. By using a toxicity value representing 30 days of exposure combined with maximum day-of-treatment turf residues, people on treated lawns were assumed to have the maximum day-of-application exposure every day for 30 consecutive days, a very health protective assumption. There were no risks of concern.

In addition to the lawn use assessment completed to support the aggregate risk assessment for this new use, a quantitative spray drift assessment specific to the new corn and soybean uses was also completed to address several comments brought up during the public comment period. This assessment used the AgDRIFT model to assess spray drift. AgDRIFT has undergone extensive validation including evaluation by a FIFRA Scientific Advisory Panel. This model quantifies residues deposited on a residential lawn that is adjacent to the field being treated. These residues were used in conjunction with the 2012 Residential SOP for turf assessment to determine exposure to children via contact of residues that have deposited on lawns via spray drift. To address specific comments submitted, the Agency conducted this assessment using a risk assessment Point of Departure (PoD) 3-fold lower (more protective) than used in the Agency assessment, and also applied the 10X FQPA safety factor. As with the turf assessment, considering the Agency's use of a toxicity value representing 30 days of exposure combined with maximum day-of-treatment spray drift residue, people on lawns exposed to spray drift were assumed to have the maximum day-of-application exposure every day for 30 consecutive days, a very health protective assumption. There were no risks of concern using even these extremely protective assumptions.

The Agency did not use AgDISP in its assessment, so comments related to use of that model are not pertinent. AgDRIFT was not used in the Agency's initial risk assessment, but was used as described above, to more fully characterize risks from drift in response to comments received on the petition. While AgDRIFT has not gone through the formal CREM (Council for Regulatory Environmental Modeling) evaluation process, it has been evaluated by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) which uses essentially the same criteria in its evaluation and found the model to be scientifically supported and sound. The AgDRIFT model is based on well-established physics, and was developed jointly by the EPA, USDA, and industry, undergoing many quality assurance steps in the process. The model is well supported by data from drift studies. For these reasons, we believe that the study has gone through sufficient review to be used in this context.

Some commenters indicated that residential exposure to 2,4-D would increase as a result of the proposed use. Since there is no change in the residential use patterns, the only potential for increased residential exposure is to bystanders exposed through drift or volatility, neither of which have risk concerns, as described above.

Comment: *The Agency's worker exposure must use maximum application rate*

Response: The worker exposure assessment was completed using the maximum application rate.

Comment: *Residential exposure will increase with this new use (2,4-D is found in carpet dust even though they had not used the pesticide recently; 2,4-D is blowing in or tracked into homes; farmer and farm families' exposures are underestimated)*

Response: EPA believes that the current method of hand-to-mouth exposure assessment for pesticide residues from applications directly to turf is protective of exposure to indoor house dust. The current approach accounts for exposure to residues immediately after a direct application is made at the maximum application rate, residues which will be much higher than those found in house dust from track-in. Furthermore, residues immediately after a direct turf application were used and compared to a toxicity endpoint representing 30 days of exposure. As discussed earlier, this results in very protective estimates of risk.

II. Environment

Another area of concern for many commenters was the risk of adverse environmental impacts from the increased application of 2,4-D. As with comments regarding human health issues, many commenters expressed similar concerns involving the environment, so the comments are grouped into major topic areas and addressed below.

A. Spray Drift

Comment: *Spray drift is a complete exposure pathway for the proposed new uses of 2,4-D. 2,4-D is known to drift and there have been numerous spray drift incidents (mainly crop damage) that have been associated with the use of 2,4-D. Drift will adversely affect sensitive crops in neighboring fields as well as endangered/threatened species or other non-target organisms. In particular, the later timing of 2,4-D applications will increase direct risk to non-target plants (indirect risks to other species that rely on plants) because application events will occur when more plants are more fully leafed out. Spray drift cannot be reasonably restricted to the field to which 2,4-D is being applied and the proposed buffer of 30 ft is too small.*

Response: The Environment Fate and Effects Division (EFED) did identify spray drift as a complete exposure pathway for non-target organisms in the original risk assessment (USEPA 2013a, D400223+). The assessment also acknowledged a large number (~460) of plant incidents as well as incidents to other non-target organisms (reported to the Agency as of

October 31, 2012). Dicotyledonous terrestrial plants were identified as the most sensitive non-target organisms and spray drift buffers of > 1000 ft were calculated to be protective. The 2,4-D choline salt itself has drift/volatility-reducing characteristics. Consequently, the assessment was refined using droplet spectrum data that were specific to the GF2726 formulation (MRID 48844001). As a result, spray drift buffer distances for the most sensitive species (dicotyledonous terrestrial plants) were reduced to 202 ft.

In June 2013, EPA issued an addendum to the original risk assessment (USEPA 2013b, D411614) that revised the terrestrial dicotyledon endpoint that was used in the risk assessment. Originally, an endpoint from a 2,4-D ester had been chosen because it was the most sensitive among all the plant data. EPA reconsidered that endpoint given that 2,4-D choline is not an ester, and changed the endpoint to reflect the most sensitive toxicity value for a 2,4-D salt or amine, consistent with the approach taken in the Registration Eligibility Decision (RED) (USEPA 2005a). Based on the 2,4-D salt/amine endpoint, spray drift buffer distances ranged from < 25 ft to 30 ft to protect the most sensitive plant species. EPA believes this new endpoint is the most appropriate and the buffers are adequate to protect the most sensitive plant species from spray drift.

After determining the appropriate buffer, EPA discussed mitigation measures with Dow AgroSciences, LLC (DAS). To confine spray drift to the field, DAS agreed to implement a 30 ft in-field buffer when the wind is blowing towards a sensitive area that could provide habitat for a non-target species. Non-sensitive areas are considered fields with crops, buildings, or pavement; all other areas constitute potential habitat for non-target species. In cases where the wind is blowing towards a sensitive area, a 30 ft in-field buffer must be implemented. The 30 ft buffer strip may be sprayed at a later time when the wind direction has shifted and is no longer blowing towards the sensitive area. EPA determined that by using this approach, any spray drift from 2,4-D choline salt remains on the corn or soybean field that is being treated.

The proposed use allows for one application pre-plant and up to two applications post-plant. The herbicide resistant traits in the genetically engineered corn and soybean plants allow the timing of the post-applications to be much later in the season (up to 48-in sized corn and flowering soybeans) than conventional corn (up to 8-in sized corn) and soybean (no post-plant applications). Potential risk concerns to non-target species were therefore considered in light of the later timing of applications of 2,4-D choline salt. For those groups of organisms identified in the original screening-level risk assessment (USEPA 2013a) as potentially at risk, the 2014 endangered species assessment (USEPA 2014, D418022) considered how the later 2,4-D application timing could affect non-target species. Using a combination of species-specific biology, diet, habits, migration, and geographic proximity, the assessment (USEPA 2014) determined that no species (terrestrial and aquatic plants, mammals, birds, reptiles, amphibians, terrestrial invertebrates, aquatic invertebrates, or fish) within the 6-state action area (Illinois, Indiana, Iowa, Ohio, South Dakota, Wisconsin) exceeded the level of concern for spray drift as established by the Agency.

B. Synergy of glyphosate and 2,4-D

Comment: *The Enlist formulation is a combination of two herbicides (2,4-D choline salt and glyphosate) as well as adjuvants and inerts. The Agency did not address the potential synergistic effects between 2,4-D choline salt and glyphosate nor potential reactions with the other chemical components of the formulation.*

Response: Although the Agency does not routinely include a separate evaluation of mixtures of active ingredients, EPA believes it adequately addressed the issue of synergism between 2,4-D and glyphosate by evaluating data on the chemicals individually as well as with formulation-specific information.

In the case of a formulation with multiple active ingredients, each active ingredient is subject to an individual risk assessment for a regulatory decision regarding the active ingredient on a particular use site. If effects data are available for a formulated product containing more than one active ingredient, they may be used qualitatively or quantitatively in accordance with the Agency's Overview Document and the Services' Evaluation Memorandum (USEPA 2004; USFWS/NMFS/NOAA 2004).

Synergistic reactions among chemicals are possible, but considered rare. For 2,4-D and glyphosate specifically, the Agency compared the Enlist Duo™ formulation-specific acute oral rat study (OPPTS 870.1100; MRID 48289803) LD_{50} of 623 mg ae/kg-bw (confidence interval of 389 to 4980) with the 2,4-D-only LD_{50} used in the assessment (441 mg ae/kg-bw) (MRID 41413501). The endpoints are similar and do not indicate a synergistic effect of 2,4-D and glyphosate for mammals.

Furthermore, EPA considered an open literature peer-reviewed published study by Abdelghani *et al.* (1997) that specifically looked at the toxicity of glyphosate/2,4-D mixture on channel catfish, bluegill sunfish, and crawfish. The experiment first tested the toxicity of 2,4-D and glyphosate individually. Then the two chemicals were mixed together in a 1:4 ratio (glyphosate:2,4-D); it is recognized that the ratio of glyphosate to 2,4-D choline salt in the Enlist Duo™ formulation (1:1) is higher. After accounting for the inherent differences in toxicity between the individual chemicals, the study concluded that no synergistic effects were observed. EPA agrees with the findings in this study that there is no synergistic interaction of 2,4-D and glyphosate for freshwater fish or freshwater invertebrates.

Given that there is no indication of synergism between 2,4-D and glyphosate for mammals, freshwater fish, and freshwater invertebrates, EPA believes it is reasonable to assume that there are no synergistic interactions for the taxonomic groups that were not tested, including plants.

C. Volatility

Comment: *2,4-D has been known to volatize under certain environmental conditions and cause damage to off-site plants. EPA's volatility assessment relied on questionable laboratory plant data. Furthermore, the volatility study used to derive a vapor flux rate*

specific to 2,4-D choline salt was not fully reviewed. Overall, there are uncertainties regarding EPA's conclusions that the volatilization exposure pathway does not present risk concerns for Enlist Duo.

Response: EFED's risk assessment considered potential effects from the volatilization of 2,4-D choline salt (USEPA 2013a) using several lines of evidence. First, data from a laboratory plant vapor study (MRID 48911801) indicated that grape was more sensitive to 2,4-D vapor than cotton, tomato, or soybean (this study was only available for qualitative use because of the methodology used to conduct the experiment). Second, data from several field studies related plant damage in grape, cotton, and soybean to growth or yield endpoints (Andersen *et al*., 2004; Everitt and Keeling, 2009; Kelley *et al.*, 2005; Marple *et al.*, 2008; Ogg *et al.*, 1991; Robinson *et al.*, unpublished). Again, grape was the most sensitive with 20% damage resulting in decreases in growth and yield (cotton ranged from 58 to 66% damage and soybean from 35 to 52% damage before decreases in yield occurred). Third, a field study (MRID 48862902) placed potted grapes and cotton on and off of a field (5 m and 15 m) that had recently been treated with 2,4-D choline salt. At the end of the 3-day exposure period and 27 day observation period, only plants placed directly on the field showed outward signs of damage (cotton – 40%; grape – 0.6%). From these three lines of evidence, a conservative plant toxicity threshold of 20% physical damage was chosen for the volatility analysis. 2,4-D choline vapor flux data from a field volatility study (MRID 48862902) was used to address exposure from volatilized 2,4-D to plants that were off the field. At the time of the ecological risk assessment, the study was under review, but preliminarily considered to be scientifically sound and appropriate for use in the risk assessment. The review of the field volatility study was completed on November 18, 2013 (USEPA, 2013c) and found acceptable for quantitative use in risk assessments. The highest 2,4-D choline flux rate from the study was used as the input parameter for two models: AERSCREEN and PERFUM. AERSCREEN predicts 2,4-D exposure from wet and dry deposition off of the field. The model indicated negligible amounts of 2,4-D would be deposited through this pathway, and thus there were no risk concerns for plants. The PERFUM model predicts the air concentration of 2,4-D that is expected at the edge of the field and various distances beyond. The results showed that the air concentrations of 2,4-D were below the 20% plant damage threshold at the edge of the field, thus indicating no risk concerns to plants from vapor exposures.

D. Data Gaps

Comment: *EPA's ecological risk assessment contained a number of ecological and fate data gaps that are usually required to be filled for outdoor pesticide use patterns.*

Response: The ecological risk assessment (USEPA 2013a) acknowledged a number of ecotoxicological and environmental fate data gaps and explained the assumptions that were made in absence of the data:

- Acute oral toxicity test for passerines: This is a generic data gap and the study has been requested as part of the Registration Review data call-in. In the absence of passerine-

specific data, EPA routinely relies on data from bobwhite quail or mallard duck as surrogate species. Data for both species were available for 2,4-D and scaled to adjust for the smaller passerine bird body size.

- Estuarine/marine invertebrate chronic toxicity test: This is a generic data gap, but the Agency has not requested the data because 2,4-D is not expected to remain in the aquatic environment long enough to result in chronic exposures. For screening-level risk assessment purposes, an acute-to-chronic ratio (commonly used to estimate missing toxicity information when toxicity information is available for similar organisms), based on freshwater invertebrates, was used to estimate the missing chronic toxicity value. Given that chronic exposures are unlikely, the Agency considers this a protective approach.
- Terrestrial plant seedling emergence and vegetative vigor tests for Enlist Duo™: This is a data gap that is specific to Enlist Duo™. Terrestrial plant data for commonly-used formulations are usually required by EPA. In the absence of formulations-specific information, EPA uses the most sensitive data from other formulations. This is a routine practice with 2,4-D and many other pesticides because data are not available for all registered formulations of 2,4-D. In this case, data from 2,4-D salts/amines were used as surrogates for Enlist Duo™. The surrogate approach assumes that although data are not available for every formulation, that the available data capture a range of toxicological responses. For 2,4-D, the Agency has a robust set of plant studies; consequently, we can be reasonably confident that by choosing the most sensitive toxicity values from 2,4-D amine/salt studies, that we are being protective. Consequently, these data are not necessary.
- Terrestrial field dissipation study with 2,4-D choline salt: This is a generic data gap for 2,4-D choline salt. The bridging strategy developed for other salt and amine forms of 2,4-D was assumed applicable to 2,4-D choline salt because the salt form is similar to other 2,4-D forms.

Comment: *In addition, data from volatility/spray drift and the Enlist Duo formulation (2,4-D choline salt and glyphosate) were not considered in the risk assessment.*

Response: Risk assessments are usually conducted on a single active ingredient basis. Consequently, mixture data for products with multiple active ingredients (*i.e.,* 2,4-D choline salt and glyphosate) are not usually required. Furthermore 2,4-D choline salt/glyphosate data for the acute oral rat study (MRID 48289803) did not show an increased toxicological response compared with the most sensitive 2,4-D endpoint that was used in the risk assessment (MRID 41413501) (see Synergism comment and response for more discussion).

EFED's assessment incorporated data from several studies into the assessment to account for spray drift and volatility. 2,4-D choline salt-specific deposition curve was developed for the AIXR 11004 nozzle to determine a spray drift buffer distance. 2,4-D choline salt vapor flux data were used in conjunction with terrestrial plant ecotoxicity data to set conservative levels of concern for adverse effects and to model whether off-field plant damage was expected to occur.

Comment: *Effects from low dose exposures may not be captured in the standard suite of ecotoxicity studies listed in Part 158 of the Code of Federal Regulations.*

Response: While studies specifically measuring low-dose effects of a chemical are usually not required by the Agency, the normal suite of toxicity studies captures this same information in the form of sub-lethal effects seen at dosing levels below the LD_{50}/EC_{25} thresholds. Sub-lethal effects are incorporated into the risk characterization section for every taxonomic group.

E. Honeybees

Comment: *Enlist Duo will contribute to the decline of honeybees and other pollinators. In particular, pesticides are a contributor to colony collapse disorder in honeybees. EPA did not follow its own Pollinator Risk Assessment Framework when conducting the risk assessment on Enlist Duo.*

Response: EPA recognizes the importance of pollinators and that colony collapse disorder is a complex phenomenon to which pesticide exposure may contribute. The Agency strives to incorporate the most up-to-date pollinator data and risk assessment practices into its analyses. The Pollinator Risk Assessment Framework was adopted in June of 2014, well after the 2,4-D choline salt risk assessment was developed [the honeybee analysis risk assessment (USEPA 2013a) applied the methodology in the RED (2005)].

Honeybee Assessment Using Pollinator Risk Assessment Framework
Honeybee data for acute contact exposures (LD_{50} > 88 µg ae/bee) and acute oral exposure (LD_{50} > 62.6 µg ae/bee) indicated that 2,4-D choline salt is "practically non-toxic" to honeybees on an acute contact basis. No laboratory data are available for chronic effects to adults or acute or chronic effects to larvae, which are considered generic data gaps for 2,4-D under the Framework (USEPA 2013a).

The environmental exposure concentration (foliar spray) for honeybee via contact exposure is 2.7 µg ae/bee. When compared with the LD_{50} of > 88 µg ae/bee for 2,4-D choline salt or the most sensitive 2,4-D value (from an ester form) of LD_{50} > 66 µg ae/bee, the estimated exposure concentration is lower than the LD_{50} threshold.

For the dietary pathway, the estimated exposure concentration for adult honeybees is 32.12 µg ae/bee/day. When compared with the LD_{50} of > 62.6 µg ae/bee, the estimated exposure concentration is about half of the LD_{50}, if taken at face value. The LD_{50} could be much larger, but this is an uncertainty given the "greater than" value derived from the honeybee acute oral toxicity study.

Considering the results of the acute contact and oral analyses conducted in accordance with the Pollinator Risk Assessment Framework, acute risk concerns to adult honeybees are not expected.

F. Dioxins and Other Chemical Impurities

Comment: *Dioxins are known to be formed during the manufacturing process of 2,4-D. The increased use of 2,4-D associated with herbicide-tolerant corn and soybean will lead to an increase in dioxins, as well as other impurities formed during the manufacturing process, in the environment.*

Response: The 2,4-D choline salt risk assessment (USEPA 2013a) evaluated the risk from polychloro dibenzo-*p*-dioxin (PCDD) and polychloro dibenzo-*p*-furans (PCDF) that may be formed during the manufacture of 2,4-D. The Agency reviewed product chemistry data for 2,4-D choline salt (USEPA 2012, D405897; Confidential memo) and found that PCDD and PCDF concentrations were lower than those identified in an earlier assessment with 2,4-D and 2,4-D ethylhexyl. The earlier assessment concluded that there were no risk concerns from these concentrations of PCDD and PCDF; thus those same conclusions hold for 2,4-D choline salt given that dioxin concentrations were even lower (USEPA 2005b, D317729).

G. Glyphosate Specific Comments

Comment: *The population of monarch butterflies is declining. Monarchs rely on milkweed for egg-laying and larval development. The widespread use of glyphosate has drastically decreased the milkweed populations as they are often found within or along the edges of agricultural fields. Enlist, which contains glyphosate as well as 2,4-D choline salt, is anticipated to further the decline of milkweed, and indirectly, the monarch butterfly. EPA's risk assessment for 2,4-D choline salt nor existing risk assessments for glyphosate did not take into account the adverse effects of Enlist on the monarch.*

Response: Glyphosate is currently undergoing Registration Review, and a draft risk assessment is scheduled for completion by December 2014. In this assessment, EPA is considering glyphosate's direct and indirect effects on monarch butterflies (including its obligate plant, milkweed) and other non-target species.

Comment: *No endangered species risk assessment has been performed for glyphosate. EPA has not examined the direct or indirect effects of the glyphosate component of Enlist for the proposed uses on herbicide-tolerant corn and soybean.*

Response: EPA did not conduct an endangered species risk assessment for the glyphosate component of the Enlist Duo™ formulation because the uses on this new formulation were not new to glyphosate. Instead, an endangered species risk assessment will be included in the final registration review decision consistent with the National Academy of Sciences (NAS) recommendations. See the response to the Endangered Species comments below. Given that the agencies are continuing to develop and work toward implementation of the NAS recommendations to assess the potential risks of pesticides to listed species and their designated critical habitat, the draft ecological risk assessment supporting the proposed interim registration review decision for glyphosate will not contain a complete ESA analysis. Once the agencies have fully developed and implemented the scientific methods necessary to

complete risk assessments for endangered and threatened (listed) species and their designated critical habitats, these methods will be applied to subsequent analyses for glyphosate as part of completing the final registration review decision.

H. General Ecotoxicity Concerns

Comment: *EPA's risk assessment states that 2,4-D is toxic to fish, aquatic invertebrates, birds, and mammals. Ecotoxicity data for plants also showed them to be sensitive to 2,4-D. In addition to mortality, many of the ecotoxicological studies documented other signs of toxicity/poisoning.*

Response: EPA requires a suite of toxicological data on mammals, birds, honeybees, freshwater fish and invertebrates, estuarine/marine fish and invertebrates, aquatic plants, and terrestrial plants. The purpose of the data is to determine the toxicity of the pesticide when direct exposures occur. This is known as "hazard" and is one of two components that make up "risk."

The second consideration is "exposure." Exposure constitutes how much of the pesticide will come into contact with an organism. "Risk" is a combination of the hazard of the pesticide and the anticipated exposure of the pesticide. For example, a pesticide that is highly toxic to mammals, but is incorporated in the ground may present low risk to mammals because most mammals would not be exposed to it.

The risk assessment for 2,4-D choline salt incorporates both the hazard and exposure components into its conclusions; thus although it may be toxic to some groups of organisms, the risk varies proportionately with exposure. In particular, the mitigation requirements (in-field buffer, wind direction, rainfastness) and drift reducing properties of the 2,4-D choline salt/glyphosate formulation made it possible to limit the exposure from spray drift to sprayed corn and soybean fields. After toxicity information and Enlist Duo^{TM} exposure were considered (USEPA 2014), EPA determined that there are no risk concerns from spray drift for any threatened or endangered species in the 6 states (IN, IL, IA, OH, SD, WI) that were assessed for this registration. From this information (USEPA 2014), EPA made a "no effect" determination under the Endangered Species Act for threatened and endangered species within these states. Additional assessments will be performed if new states are added to the registration.

See also Comment K. below.

I. Registration Review

Comment: *2,4-D and glyphosate are currently undergoing Registration Review. EPA should delay its decision until the comprehensive Registration Review risk assessments, including endangered species, have been completed for both chemicals.*

Response: The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended by the Food Quality Protection Act (FQPA) of 1996, mandates the continuous review of existing pesticides. The Registration Review program is intended to make sure that, as the ability to assess and reduce risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. The Agency periodically reevaluates pesticides to make sure that products in the marketplace can continue to be used safely. During this process, label revisions, mitigation measures, and other registration changes are equitably applied to all registrations and registrants.

As noted in an earlier comment (above), EPA is currently reviewing glyphosate within the framework of the Registration Review risk assessment process. This analysis will consider the available data to assess exposures that may cause direct and/or indirect effects to taxa, including non-target organisms such as the monarch butterfly. EPA intends to issue a draft risk assessment by the end of December 2014. Once the agencies have fully developed and implemented the scientific methods necessary to complete risk assessments for endangered and threatened (listed) species and their designated critical habitats, these methods will be applied to subsequent analyses for glyphosate as part of completing this registration review.

2,4-D began the Registration Review process in 2012 and is currently receiving and reviewing data submitted by registrants as a result of the data call-in. Given that Registration Review is a lengthy process that may take many years to complete, the Agency's policy is to continue to make registration determinations for new actions during this process. Proposed new registrations are held to the most current data requirements and up-to-date risk assessment practices and must meet the FIFRA no unreasonable adverse effects standard to be registered.

J. Water Quality

Comment: *2,4-D is likely to leach to aquatic environments because of its low soil-adsorption coefficient. Increased use of 2,4-D will lead to elevated surface water pollution, which will affect the quality of water near agriculture as well as non-target organisms.*

Response: The ecological risk assessment considered 2,4-D exposure to aquatic non-target organisms. The Pesticide Root Zone Model and Exposure Analysis Modeling System (PRZM/EXAMS) was used to estimate conservative environmental exposure concentrations (EECs) based on the environmental fate properties, proposed crops, and application methods and rates of 2,4-D choline salt. These EECs are then compared with ecotoxicity information for fish, aquatic invertebrates, aquatic plants, and terrestrial plants to identify potential risk concerns.

The 2,4-D choline salt assessment also considered real-world monitoring data. Formulated 2,4-D rapidly dissociates into its acid form, so the available monitoring data are not specific to any formulated products. However, 2,4-D acid concentrations in surface water from 2,4-D choline is expected to be lower than other formulated products because of its application restrictions (*i.e.,* ground applications only; nozzle and pressure restrictions).

Monitoring data from the United States Geological Survey's (USGS) National Water Quality Assessment Program (NAWQA), indicate that 2,4-D is present in groundwater (concentrations up to 1.4 µg ae/L) and surface water (concentrations up to 8.7 µg ae/L). These concentrations are much lower than the 58 µg ae/L that was predicted as the exposure value using PRZM/EXAMS and subsequently used in the risk assessment. The monitoring data showed that 2,4-D is being detected at concentrations that are below the values that are being predicted by EPA's computer simulation models. Consequently, EPA is being protective by using the modeled number (58 µg ae/L) versus the monitoring number (8.7 µg ae/L). The Agency recognizes that the NAWQA monitoring data may not capture the highest 2,4-D concentrations in the environment, but they would need to be an order of magnitude higher to approach the modeled concentration. Using the 58 µg ae/L from PRZM/EXAMS, no direct risk concerns were identified for aquatic taxa (USEPA 2013a).

K. Risk Determinations and Endangered Species Assessment

Comment: *EPA's risk conclusions for listed and non-listed species are flawed.*

Response: The Agency will address each item under this comment specifically. The Agency has concluded that it conducted the risk assessment consistent with its policies and guidance in place at the time of the submission of the proposal for registration.

Comment: *The assessment did not consider 2,4-D choline salt degradates, of which 2,4-DCP may be more toxic to some organisms.*

Response: The initial ecological risk assessment considered 2,4-DCP, a major degradate of 2,4-D choline salt, in its analysis. Peer reviewed literature and data presented on the European Footprint Database indicate that 2,4-DCP may be more toxic to freshwater fish and invertebrates than 2,4-D. Table 30 in the assessment compares the 2,4-DCP toxicity endpoints with the predicted environmental concentrations of 2,4-DCP, based on PRZM/EXAMS (USEPA 2013a). The toxicity values are several orders of magnitude higher than the estimated environmental concentrations. Consequently, risks to aquatic organisms are not a concern from 2,4-DCP.

Comment: *Effects to migratory birds were not assessed, as required, under the Migratory Bird Treaty Act.*

Response: Migratory birds are assessed as part of EFED's standard screening-level risk assessment process. Migratory birds are included in the risk conclusions for non-listed birds (for those species that have not been designated as threatened or endangered under the Endangered Species Act), and listed birds (for those species that are threatened or endangered). Acute exposure risk concerns were identified for both listed and non-listed birds in the screening level assessment. The refined endangered species spray drift risk assessment (USEPA 2014) for the six states (IN, IL, IA, OH, SD, WI) made a "no effect" determination for threatened and endangered birds. A memorandum of understanding (MOU) on the Migratory Bird Treaty Act between EPA and the Department of Interior's Fish and

Wildlife Service is in development; the public comment period ended March 7, 2014 (EPA-HQ-OPP-2013-0744 at www.regulations.gov). The 2,4-D choline salt risk assessment is in accord with the process outlined in the MOU.

Comment: *Direct and indirect effect determinations were not made for all species.*

Response: EPA's ecological risk assessment considered both direct and indirect effects to non-target organisms. Indirect effects occur when a species that is not directly affected by the pesticide use rely upon a species that is directly affected. For example, monarch butterfly larvae rely on milkweed for food. If an herbicide kills the milkweed (direct effect on the milkweed), the monarch butterfly may be indirectly affected because its food source has been affected. In the case of the 2,4-D choline salt assessment (USEPA 2014), no indirect effects to endangered or threatened (listed) species were identified based on mitigation measures to limit spray drift exposure to only corn and soybean fields based on species biology and species proximity. Indirect effects to non-listed species would be limited to those species that rely on other non-listed species for food, habitat, or other resources. By requiring pesticide application restrictions that limit off-site exposure to levels below effects thresholds of the most sensitive taxonomic group, the action area (the geographic extent to where effects can reasonably be expected to occur), is limited to the directly treated footprint of the soy or corn field. Consequently, no direct or indirect effects are expected for threatened and endangered species (USEPA 2014) (Addendum to 2,4-D Choline Salt Section 3 Risk Assessment: Refined Terrestrial Plant Exposure Estimates and Effects Determination).

Comment: *EPA did not adequately address risk concerns from runoff.*

Response: EPA acknowledges that these public comments on the risk assessment and effects determination pointed out that the Agency did not explicitly include a consideration of the risk findings for non-target plants as a result of off-field runoff. The Agency considered the spray drift exposure to be the principal risk issue associated with the proposed labeled use of 2,4-D choline, owing to a variety of lines of evidence, including past experience with other 2,4-D formulations and associated spray drift incident reporting. However, in light of these public comments, the Agency reconsidered the runoff risks and the effects of the proposed mitigation to limit off-site runoff in listed species effects determinations.

For this registration action, spray drift and runoff were considered as exposure pathways for 2,4-D choline to terrestrial plants and aquatic organisms. For aquatic organisms, the consideration of both spray drift and runoff loadings to surface waters did not trigger concerns. Risk concerns from spray drift to terrestrial plants were mitigated with an in-field 30-foot buffer that takes into account wind direction during application, and this mitigation yielded no spray drift concerns off field, when incorporated into spray drift modeling.

The in-field spray drift buffer does not mitigate concerns from runoff because 2,4-D choline can be applied up to the edge of the field when the wind is not blowing in that direction; there is no "buffer strip" between the edge of the field and sensitive habitat. The Agency does not currently have a tool to evaluate the effectiveness of buffers in reducing pesticide exposure

via runoff. The Agency has implemented vegetative buffer or filter strips in a few instances to lessen herbicide loading in runoff waters, however in this case there are no risk concerns for aquatic organisms. To assess exposure to terrestrial plants the Agency looked at several lines of evidence to determine potential effects as described below.

2,4-D is absorbed by both shoots and roots and is active at the growing points of the shoot and root. Translocation to the site of action is primarily via the symplastic pathway (with photosynthates in the phloem) and accumulates principally at the growing point of the shoot and root. 2,4-D is not translocated as well in the apoplast (carried with the water and nutrients in the xylem), which would occur with root uptake. Therefore, growth inhibition tends to be more pronounced with foliar uptake than with root uptake (Shaner 2002). Consequently, 2,4-D in runoff waters would not be readily available for mature plant uptake. The Agency is including a statement on the label based on the rainfast period for 2,4-D that prohibits the application of Enlist Duo if rain or irrigation is expected within 24 hours. A rainfast period is the time required for the herbicide to be absorbed into the plant after application and before a rain/irrigation event so as to provide reasonable weed control. The provision of a labeled rainfast period would increase the time available for on-field herbicide adsorption, thereby reducing the amount available for runoff. This, in combination with 2,4-D's limited uptake by roots of terrestrial plants, is anticipated to reduce the amount of 2,4-D choline salt that could adversely affect plants via runoff.

Further, EPA has evaluated the assumptions regarding runoff of 2,4-D from treated fields to adjacent terrestrial habitat. The model TerrPlant assumes, for a chemical with the solubility of 2,4-D in the most mobile acid form, that runoff would amount to 5% of the field applied mass of the herbicide. This modeling approach does not account for pesticide degradation and for pesticide partitioning. These processes that account for loss are important in the mechanistic pesticide runoff models used by EPA (Pesticide Root Zone Model (PRZM)) and in the field. The Agency has compared the TerrPlant assumption of 5% runoff to the runoff predictions for PRZM runs used to characterize pesticide runoff for aquatic exposure. This comparison revealed that runoff predicted by TerrPlant for 2,4-D is grossly overestimated. The total annual runoff is less than a fifth of the amount predicted by TerrPlant for a single runoff event.

In light of these additional lines of evidence, combined with proposed mitigations such as a mandatory rainfast period, the Agency has determined that risks to terrestrial plants from runoff as predicted by TerrPlant modeling are grossly overestimated in the case of 2,4-D choline and a finding of no effects to listed or non-listed species off the treated field is appropriate.

Comment: *The risk assessment analyses did not follow the National Academy of Sciences (NAS) recommendations. The assessment dismissed risks, even when risk quotients were above the level of concern and failed to come to a "may affect" conclusion, when any risk concerns were identified.*

Response: EPA acknowledges that it did not follow the NAS recommendations when evaluating whether the 2,4-D choline salt formulation would affect listed species. However, EPA's determination of "no effect" (USEPA 2014) (Addendum to 2,4-D Choline Salt Section 3 Risk Assessment: Refined Terrestrial Plant Exposure Estimates and Effects Determination)was based on a scientifically valid methodology consisting of an ecological risk assessment conducted in accordance with Agency guidance at the time of drafting the risk assessment and consistent with the methods described in the "Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, U.S. Environmental Protection Agency: Endangered and Threatened Species Effects Determinations," Office of Pesticide Programs 2004 Overview Document. This assessment included a problem formulation describing the nature of the Federal action, an assessment of potential pesticide exposure, an assessment of the toxicological hazards associated with the pesticide, and a risk characterization that integrated all available lines of evidence to support the effects characterization for each taxonomic group and species. Moreover, in situations where there was a potential taxonomic concern, the Agency used available U.S. Fish and Wildlife Service information (i.e., Species Recovery Plans, Species 5-Year Reviews) to conduct focused assessments for individual species.

The National Academy of Sciences' (NAS) report was issued in 2013, after the screening level ecological assessment for 2,4-D choline salt was finalized. EPA and the U.S. Fish and Wildlife Service and the National Marine Fisheries Service have adopted a "day forward" approach for endangered species risk assessments that will begin once consensus is reached on the risk assessment methodology and process. Thus, the analyses used in the 2,4-D choline salt assessments (USEPA 2014) (Addendum to 2,4-D Choline Salt Section 3 Risk Assessment: Refined Terrestrial Plant Exposure Estimates and Effects Determination), use a combination of "old" methods alongside some tools that are being considered for the revised endangered species risk assessment approach.

The assessment process employed in the effects determination is composed of three parts: (1) the original screening-level assessment conducted under the provisions of the Overview Document , (2) a plant endpoint/spray drift addendum that further characterized plant endpoints taking into account all available toxicological information, and (3) an endangered species risk assessment addendum that used the results of the screening risk assessment, drift effects addendum and information on the biology (e.g. food requirements and habitat needs) for each species within the proposed action area to determine if pesticide exposure would have a direct or indirect effect on each species.

The screening level assessment (USEPA 2013a) considered risks to all non-target taxonomic groups of organisms in a manner consistent with the pre-NAS risk assessment process used to support effects determinations. That process uses available environmental fate and effects information to make preliminary determinations of whether conservative estimates of pesticide exposure would raise concerns for one or more taxonomic groups. The screening assessment results suggested that, should actual exposures occur, direct effects may be possible only for mammals, birds, reptiles, land-phase amphibians and terrestrial plants (risk quotients were above the level of concern). However, additional information related to

specific species within these taxonomic groups was needed to ascertain if species biology, geography and timing would lead to a determination that exposures would reasonably occur for these organisms. Additional information included: species specific biology, geographic location, and the ability of spray drift mitigation measures to reduce the geographic extent of exposures of concern to a limit of the boundaries of the treatment site. When these types of information were considered, the endangered species assessment addendum (USEPA 2014) (Addendum to 2,4-D Choline Salt Section 3 Risk Assessment: Refined Terrestrial Plant Exposure Estimates and Effects Determination) concluded that there were no direct risk concerns for mammals, birds, reptiles, land-phase amphibians, and terrestrial plants.

Comment: *Disagreement with the process used to reach a "no effects" determination for threatened and endangered species.*

Response: In conducting the effects determinations, the Agency used the most sensitive taxonomic group effects thresholds to establish the extent to which effects were possible (USEPA 2014). This approach is consistent with both the Overview Document approach and the NAS approach for defining the action areas of the proposed Federal action, when spray drift mitigation measures were taken. Mitigation steps were incorporated into modifications of the proposed Federal action and were incorporated into the risk screening risk assessment that was used as a quantitative input to the effects determinations. Environmental exposures, through the action of proposed mitigation (USEPA 2014), were concluded to be below effects thresholds – the no effect threshold for the most sensitive taxa for areas off the field. This effectively limited this action area of the Federal action to within the bounds of the specific target crop application sites for the pesticide product. Using the process outlined in the Overview Document for the remaining species within the action area, the Agency conducted additional exposure and effects assessment and biological evaluation (USEPA 2014), specific to those species, to determine if effects would occur for those species and to assess whether habitat utilization of the cropped areas was such that herbicide application would result a species relevant effects. See also the comment response on runoff.

Comment: *The number of uncertainties in the risk assessment reduces the confidence in its conclusions.*

Response: The agency believes that despite uncertainties, the conservative nature of the exposure and hazard evaluations as well as the careful consideration of species biology and habitat uses are sufficient to reason that the assessment is reasonable.

III. Other Concerns

A. Labeling

Comment: *The label language regarding the required spray drift buffer was unclear. More specifically, label language concerning the buffer in relation to wind direction needed clarification.*

Response: EPA has worked with the registrant to clarify the intent of this restriction, and to eliminate any confusion that may arise from the buffer label language. The intent of the label is to require a 30 foot in-field buffer at the downwind edge of the field. For example, if the wind is blowing in a southern direction, the buffer would be the 30 foot section of the corn or soybean field to be treated at the southern edge of the field. Therefore the label contains the modified language to read as follows:

You must maintain a 30 foot downwind buffer (in the direction in which the wind is blowing) from any area except:

- Roads, paved or gravel surfaces.
- Planted agricultural fields. (Except those crops listed in the "Susceptible Plants" section)
- Agricultural fields that that have been prepared for planting.
- Areas covered by the footprint of a building, shade house, green house, silo, feed crib, or other man made structure with walls and or roof.

To maintain the required downwind buffer zone:

- Measure wind direction prior to the start of any swath that is within 30 feet of a sensitive area.

- No application swath can be initiated in, or into an area that is within 30 feet of a sensitive area if the wind direction is towards the sensitive area.

EPA also suggested that Dow AgroSciences develop a diagram to clarify this issue which they have added to the label. Please see the buffer diagram on the final approved label in the docket.

Comment: *The restriction of application of Enlist Duo to only one nozzle type and pressure combination does not allow the grower adequate flexibility to other low drift nozzle technologies.*

Response: The registrant has submitted additional data to demonstrate the drift potential of the Enlist Duo™ technology applied with a variety of different nozzles. After careful review of the data, EPA has determined that additional nozzles provide the same or better drift protection as the specific nozzle originally proposed with the registration. As a result, 22 additional nozzles have now been added to the label, providing additional flexibility for the grower. More nozzles can be added to the label, as appropriate, as additional data is submitted that demonstrates at least the same drift reduction properties. See the final approved label for exact nozzle specifications.

Comment: *This product should not be restricted to use in only 6 states when the need for weed resistance management is not limited to these six states alone.*

Response: EPA is currently conducting additional evaluations to assess the use of Enlist Duo™ in the remaining corn and soybean growing states.

B. Registration

Comment: *EPA should not delay the expected timing of this action provided by the Pesticide Registration Improvement Act (PRIA) by the development of endangered species assessments and weed resistance stewardship plans.*

Response: EPA has noted the potential for higher acreage that may result from the amended use of 2,4-D that could lead to increased exposure to non-target species. The increase in acres where this pesticide could be applied could also select for weeds that develop resistance to the herbicide, therefore EPA determined that management of weed resistance in order to prolong the effective use of existing herbicides and allow growers the tools necessary to manage America's food supply must be addressed in this registration decision. Although PRIA does stipulate timeframes deemed necessary to conduct assessments and make regulatory decisions for routine applications of various pesticide actions, it does not supersede the Agency's responsibility to ensure that regulatory decisions meet the standards for registration. There are occasions when an action is more complex than expected by the PRIA timeframes. In these instances, the Agency will typically renegotiate the timeframe with the registrant to describe the additional time that is needed for a complete evaluation and to allow the additional work to be completed. The Agency will only issue a regulatory decision once all assessments deemed necessary are carefully and thoroughly completed, providing a full understanding of the potential risks and benefits of a pesticide use.

Comment: *An increase in glyphosate use could occur with the registration of Enlist Duo. Therefore, glyphosate should be assessed when considering the registration of Enlist Duo.*

Response: The registration of Enlist Duo™ does not represent any new exposures or increase in exposures for glyphosate. Glyphosate is already used on the majority of corn and soybean production acres in the United States today. Glyphosate is presently being applied in the same fields where Enlist Duo™ applications would be expected, using the same application methods as registered for Enlist Duo™. Since the use of Enlist Duo™ would represent an alternative to other registered glyphosate products that already apply glyphosate in the same manner, it would be considered to be a substitute for another equivalent glyphosate application and not an additional one.

Comment: *The use of products containing non-choline 2,4-D on Enlist crops could occur and resulting damage to other crops from drift may occur.*

Response: Enlist Duo™ provides benefit to the grower by allowing the application of the choline salt of 2,4-D at a later growth stage for corn and soybeans, providing control of problem weeds that are present during this application timing. No other 2,4-D product is registered for use on corn and soybeans during this specified time period. EPA notes that it is

a violation of Federal Law to use a pesticide not in accordance with its label. EPA prosecutes illegal use of pesticides to strongly dissuade and correct for any illegal activity.

In addition, although not required by EPA, the Agency is aware of contractual agreements that Dow AgroSciences has developed in a technology use agreement that is legally binding between the grower and the registrant. This contract prohibits the use of 2,4-D products without the choline salt technology on any Enlist seed. If violations to this contract are detected, it is EPA's understanding that DAS reserves the right to discontinue the sale of the seed to any grower who does not comply with this requirement.

Comment: *Enlist Duo may contribute to the weed resistance problem that has been caused by older products labeled for use on GE crops in general, especially those that are known to have aided in widespread weed resistance historically.*

Response: EPA and other stakeholders have studied the resistance problems associated with glyphosate and other pesticides, and EPA has worked with Dow AgroSciences to develop a robust resistance management stewardship plan designed to address this concern. In addition, because the issue of weed resistance is an extremely important issue to keep under control and can be very fast moving, this registration will expire in either 5 years (if there is use of the product on 100,000 or more acres in the first year) or 6 years (if there is use of the product on less than 100,000 acres in the first year) unless this term is removed or modified by EPA. This will ensure that EPA retains the ability to easily modify the registration or allow the registration to terminate if necessary.

C. Benefits of Registration of Enlist Duo™

Comment: *The BEAD benefits memo (April 30, 2014) stated that registration of Enlist Duo would save costs for farmers in controlling glyphosate-resistant weeds. However, if these resistant weeds are in fields, then application of the dual active ingredient product essentially has only one effective herbicide active ingredient. BEAD stated that this scenario would likely require additional herbicide mode(s) of action. This situation would negate the benefit of a dual active ingredient product and would result in more cost to the user.*

Response: The Agency's assessment outlined the general benefits of the Enlist Duo™ technology and identified benefits beyond Enlist Duo™'s ability to manage weeds already resistant to glyphosate. The benefits included increased flexibility to corn and soybean growers, a new tool for broadleaf weed control in herbicide-tolerant soybean, improved ability to manage broadleaf weeds already resistant to glyphosate or other herbicides, and in some cases, extending the viability of glyphosate.

The Agency acknowledges that in cases where resistance to 2,4-D or glyphosate exists, measures must be taken by the herbicide's users to avoid selection for resistance (e.g. add an additional effective mechanism of action). The benefits document states:

"While there are benefits to the proposed use of Enlist Duo™ in the Enlist™ system, it will be important that the system be supported by an active stewardship program as well as a robust program of early intervention and remediation when a lack of herbicide efficacy may be an early sign of resistance developing."

Therefore, the Agency is requiring that DAS have an Herbicide Resistance Management (HRM) Plan in place, which includes education and outreach programs. The HRM Plan, which is detailed in the final decision, will involve DAS working with growers to help identify early signs of weed resistance and to resolve the problem before it spreads. The HRM Plan also requires education and reporting to the Agency.

Comment: *Although the development of resistance to one or more of the active ingredients in Enlist Duo is possible, the potential for resistance development does not eliminate the utility of the product if it is used according to an appropriate management plan.*

Response: The Agency agrees with the comments. As described in its benefits analysis of April 30, 2014, the Agency believes that the registration of Enlist Duo™ would provide weed control benefits to some soybean and corn growers. Also, the registration requires an Herbicide Resistance Management (HRM) Plan that is designed to provide early warning of likely resistance. Moreover, this HRM Plan includes the registrant being proactive in addressing local reports of likely resistance, including investigation, remediation assistance, and reporting. Also, education of users of Enlist Duo™ in resistance management is required.

D. Resistance Management – Enlist Duo™ Use Practices in the Field

Comment: *Certain parts of the use directions described in the proposed decision were overly prescriptive and would not allow growers the flexibility needed to use the herbicide product effectively (e.g., the requirement for growers to scout fields 7-21 days following application). Growers' privacy rights could be at risk due to the requirement for the registrant to investigate reports of lack of herbicide efficacy, or that the Agency could strictly enforce some of the detailed practices described on proposed labels.*

Response: The Agency considered these concerns and determines that these types of labeling requirements are not necessary to ensure that the use of the product not result in resistance to certain weeds. Instead, EPA is placing the burden on the registrant through its stewardship plan and other regulatory measures in the registration. Although the scouting labeling requirement has been removed, the Agency firmly believes that it is a good best management practice to scout fields before and after herbicide application, which is consistent with integrated pest management (IPM) and is essential to early identification of lack of herbicide efficacy that could be an early sign of weed resistance. The critical importance of scouting is widely recognized by research and extension specialists in pest control and should be practiced when using Enlist Duo™ or other pesticides. However, the Agency also recognizes that on-field weed resistance is best managed by the grower who understands his or her specific situation. Therefore, the requirement to scout fields 7-21 days after application will

not be imposed, but the labels will contain recommendations for field scouting. This scouting will be specific to Enlist Duo™ and will be designed to ensure proper use of the herbicide and to detect lack of efficacy quickly so that potential resistance can be managed effectively. The Agency is confident that field scouting programs designed by the registrant will be flexible and will respect the privacy rights of individual growers.

Comment: *The term "eradicate" in the proposed decision, i.e., "DAS [the Enlist Duo registrant] must take immediate action to eradicate likely resistant weeds in the infested area" (emphasis added) is not practical. Also, in many cases, a lack of weed control following an herbicide application is a result of other factors, not a lack of herbicide efficacy.*

Response: The Agency agrees that the term "eradicate" is not appropriate in this context. Moreover, it does not adequately convey the Agency's intent. The Agency believes that areas where there is a lack of herbicide efficacy (not due to other mechanical or environmental causes) must be managed aggressively to minimize the potential for resistance to develop and spread. In areas where the most likely cause of poor weed control is a lack of herbicide efficacy, steps must be taken to destroy likely resistant weeds. Moreover, when weed populations that may be developing resistance are observed, the registrant will become actively involved with growers to ensure that these populations were managed properly. There will also be a requirement for the registrant to report to the Agency and to stakeholders when incidents of unresolved likely resistance are identified.

The Agency recognizes that many incidents of lack of weed control are not related to possible resistance. Rather, lack of weed control may be due to factors such as unexpected rain, a clogged nozzle, a missed spot on the field, or other equipment-related problem. In these cases, the Agency recognizes that on-site investigation and follow up by the registrant are not necessary.

E. Stewardship: Education and Training

Comment: *Stewardship efforts, including education and training programs, are needed to ensure proper use of Enlist Duo, as growers may rely too heavily on Enlist Duo in weed control programs. In these cases, the potential to select for resistant weeds will be greater. Stewardship programs should be flexible and facilitate local management of resistance. Also, the approach to education and training should be generally consistent for pesticides. Responsibility for oversight for education and training requirements was not clear in the proposed decision.*

Response: The Agency agrees that the registration of Enlist Duo™ for use on Enlist seed presents the potential for growers to over-rely on a single product that contains two herbicidal active ingredients. If it happens, the over-dependence can increase the selection pressure on weeds and lead to resistance. Because herbicide use on herbicide-resistant crops presents this increased risk, the Agency is addressing resistance potential in this registration in an unprecedented manner.

The terms of registration for Enlist Duo™ place the responsibility on the registrant for reducing the potential for resistance or to significantly delay the onset of resistance. The Agency is also requiring the registrant to develop education and training programs that will provide growers with the best available information on herbicide resistance management. Although requiring the registrant to provide education and training, the Agency has not imposed label or use restrictions on the grower, enabling him or her to exercise flexibility in weed control practices based on local conditions.

F. Reporting

Comment: *The reporting requirements outlined in the proposed decision were overly strict and could actually deter growers from reporting likely resistance to the registrant. The registrant should report confirmed resistance to the Agency through adverse effects reporting required in section 6(a)(2) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).*

Response: The Agency believes that timely and accurate reporting is needed to fully understand the nature and extent of possible resistance that may develop as a result of Enlist Duo™ use. The Agency believes that growers will be the first ones to recognize the early signs of herbicide resistance. Therefore, the Agency has specified in the terms of registration that it must be easy for growers to report the early signs of resistance to the registrant. The Agency has not mandated specific reporting requirements for growers. Further, the Agency believes it is common practice for growers to readily report the early signs of resistance to the chemical dealer or the registrant.

Instead of placing the burden on the growers, the Agency has determined that the registrant must report to the Agency on a regular basis concerning likely resistance. These reports are needed by the Agency to facilitate its understanding of whether resistance may be developing and, if it is, its severity and geographic distribution. Also, the registrant will be required to report likely resistance to growers who could be affected so they can take appropriate measures to minimize the impact of resistance on their crop production.

The Agency agrees that confirmed resistance must be reported under FIFRA section 6(a)(2). However, it may take several years before resistance is confirmed even though its early signs appeared much sooner. The Agency therefore is requiring the specific reporting described in the final decision. This early warning can help growers understand the potential for resistance to develop and also serve as an early warning system if resistance is found nearby.

G. Other Comments

Comment: *The Agency should consider the Agricultural Biotechnology Stewardship Technical Committee (ABSTC) model for resistance management for Enlist Duo. This model has been adopted for plant-incorporated protectants (PIPs) such as Bt crops. ABSTC is an industry-led structure which is preferable to the proposed registration decision for Enlist Duo which*

appeared to place more responsibility on the grower and makes him or her liable for a lack of compliance.

Response: The Agency agrees that the ABSTC model, if modified for an herbicide registered for use on an herbicide-tolerant crop, is relevant for Enlist Duo™. The ABSTC model was consulted when determining the appropriate terms of the registration for the Enlist Duo™ product. In addition, the Agency is requiring registrants to implement practices intended to facilitate early identification of possible resistance, to remediate lack of herbicide efficacy that could be the start of resistance, follow-up, and reporting. Further, the Agency has not mandated specific practices on labels, thereby allowing maximum flexibility for users of Enlist Duo™.

Comment: *New resistance management requirements for Enlist Duo should also apply for other products and for future registrations as well. Also, the many registrations for 2,4-D and glyphosate make it difficult to address related resistance issues when this proposal applies only to Enlist Duo.*

Response: With the registration of Enlist Duo™, the Agency is establishing a new approach for resistance management for herbicides registered for use on herbicide-tolerant crops. Future registration actions for herbicides used on herbicide-tolerant crops will be patterned after the Enlist Duo™ decision. The Agency will use the registration review process to address resistance managment for the existing registrations of 2,4-D, glyphosate and other herbicides where resistance is an important issue.

Comment: *From 1993 to 2008-2009 there has been approximately a 10-fold increase in the amount and acreage of glyphosate use. In some cases where Enlist Duo may be used, glyphosate-resistant weeds are already present, and resistance to 2,4-D may develop.*

Response: The Agency agrees that glyphosate use has substantially increased since the early 1990s. However, the Agency does not believe there will be an increase in glyphosate use resulting from this action because glyphosate is already used extensively on corn and soybean.

The Agency agrees that Enlist Duo™ may be used on fields where glyphosate resistance is already present. In some of these cases, judicious use of Enlist Duo™ may help manage the glyphosate resistance. However, care must be taken by the herbicide user to carefully manage the potential for these glyphosate-resistant weeds to become resistant to the 2,4-D component of Enlist Duo™. In such cases, the DAS stewardship program will educate the user on the importance of using diverse methods of weed control to reduce the likelihood of 2,4-D resistance developing.

Comment: *Although EPA has recognized that glyphosate-resistance is an important issue, it is not approaching the problem appropriately. Rather than "taking a step back" and reevaluating the GE strategy, the Agency is "rushing" to approve a technology that will continue the "pesticide treadmill" with increased resistance now to 2,4-D.*

Response: The Agency recognizes that the development and spread of herbicide resistant weeds is an important issue for all herbicides, not just for glyphosate and 2,4-D. The presence of herbicide resistant weeds results in increased costs of production to the grower, increases the difficulty of managing crop production, and can require control measures that may have negative effects on the environment (e.g., requiring cultivation that could increase soil erosion).

After extensive analysis and review, the Agency has determined that Enlist Duo™ meets the statutory criteria for registration. Further, the Agency has required as part of the terms and conditions of the Enlist Duo™ registration that the registrant proactively manage the potential development of resistance.

Comment: *While registrants for new auxin-based herbicides claim resistance is unlikely, they leave out that 1) a similar argument was made prior to glyphosate release, 2) it is not the case that "very few" weed species are resistant to 2,4-D—worldwide there are 16 species resistant to 2,4-D, and 3) while the theory that weeds are statistically less likely to develop resistant to two herbicide active ingredients—the fact that the glyphosate-resistant population in some fields is so great that there is a high likelihood that exposure to 2,4-D will result in populations resistant to 2,4-D as well as glyphosate. In addition, these fields are most likely to be planted with stacked tolerant GM crops.*

Response: The Agency agrees with the commenter's concern over the potential for weed resistance development, especially to multiple mechanisms of action. The terms of registration and stewardship requirements are intended to provide early warning and allow for timely intervention when likely resistance is detected. The Agency recognizes that where glyphosate resistance is already present, the 2,4-D component of Enlist Duo™ will only be effective against the broadleaf weeds. In those cases, the Agency will require that the registrant's stewardship plan alert growers to the special problem of glyphosate resistance and provide the grower with education and training to use best management practices that will reduce the probability of resistance to 2,4-D.

Comment: *Traditionally, 2,4-D was registered for use as a single preplant herbicide on cereal fields. The new GM crop will allow higher rates, more applications, in successive crops, over a wider area than currently. Therefore, the potential is high for greater development of resistance to 2,4-D (and other auxin-based herbicides).*

Response: The Agency agrees that there is the potential for resistance to develop as a result of over-use of Enlist Duo™, or using it without best management practices. Therefore, the Agency is requiring the registrant to develop an extensive stewardship program to educate users of this problem. Moreover, through the terms of registration for Enlist Duo™, the Agency is requiring the registrant to undertake several steps that are intended to provide early detection and remediation in cases where a lack of herbicide efficacy may be an early sign of resistance developing.

Comment: *Starlink™ was also regulated but the release failed. What is different about Enlist Duo's possible release?*

Response: The StarLink™ issue related to the release of genetically-modified corn that was not approved for human consumption. That situation, and the circumstances surrounding it, is not comparable to the Agency's action on Enlist Duo™. The USDA Biotechnology Regulatory Services has jurisdiction over the deregulation of the Enlist corn seed. The Agency's action is limited to the registration of Enlist Duo™, the herbicide product that is intended for use on corn and soybean crops grown from Enlist seed.

Comment: 2,4-D usage was estimated to increase 3 to 7 times by 2020 in the USDA 2014 Environmental Impact Statement. As a result of this increased usage the evolution of 2,4-D resistance will be facilitated and will result in changes of conservation tillage practices.

Response: The Agency agrees that there will be increased usage of 2,4-D because of the longer period of time that applications can be made in corn and that for the first time, up to two applications can be made over-the-top in soybeans. Increased usage of 2,4-D was fully accounted for in the risk assessments that the Agency has conducted for Enlist Duo™. Further, because of the likelihood of the development of resistant weeds and their associated impacts, the Agency has established and implemented its new herbicide resistance management approach as described in the Final Registration of Enlist Duo™ Herbicide, dated October 14, 2014.

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Exhibit P

***NATURE* | NEWS: EXPLAINER**

Widely used herbicide linked to cancer

As the World Health Organization's research arm declares glyphosate a probable carcinogen, *Nature* looks at the evidence.

Daniel Cressey

24 March 2015

Daniel Acker/Bloomberg/Getty

Glyphosate, a chemical found in Monsanto's 'Roundup' herbicide product, has been declared "probably carcinogenic to humans".

The cancer-research arm of the World Health Organization last week announced that glyphosate, the world's most widely used herbicide, is probably carcinogenic to humans.[1] But the assessment, by the International Agency for Research on Cancer (IARC) in Lyon, France, has been followed by an immediate backlash from industry groups.

On 23 March, Robb Fraley, chief technology officer at the agrochemical company Monsanto in St Louis, Missouri, which sells much of the world's glyphosate, accused the IARC of "cherry picking" data. "We are outraged with this assessment," he said in a statement. *Nature* explains the controversy.

What does the IARC report say?

The IARC regularly reviews the carcinogenicity of industrial chemicals, foodstuffs and even jobs. On 20 March, a panel of international experts convened by the agency reported the findings of a review of five agricultural chemicals in a class known as organophosphates. A summary of the study was published in *The Lancet Oncology*[1].

Two of the pesticides — tetrachlorvinphos and parathion — were rated as "possibly carcinogenic to humans", or category 2B. Three — malathion, diazinon and glyphosate — were rated as "probably carcinogenic to humans", labelled category 2A.

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Why should I care about glyphosate?

Glyphosate is the world's most widely produced herbicide, by volume. It is used extensively in agriculture and is also found in garden products in many countries. The chemical is an ingredient in Monsanto's weedkiller product Roundup, and glyphosate has become more popular with the increasing market share of crops that are genetically engineered to be tolerant to the herbicide.

What evidence is there for a link between glyphosate and cancer?

The IARC review notes that there is limited evidence for a link to cancer in humans. Although several studies have shown that people who work with the herbicide seem to be at increased risk of a cancer type called non-Hodgkin lymphoma, the report notes that a separate huge US study, the Agricultural Health Study, found no link to non-Hodgkin lymphomas. That study followed thousands of farmers and looked at whether they had increased risk of cancer.

But other evidence, including from animal studies, led the IARC to its 'probably carcinogenic' classification. Glyphosate has been linked to tumours in mice and rats — and there is also what the IARC classifies as 'mechanistic evidence', such as DNA damage to human cells from exposure to glyphosate.

Kathryn Guyton, a senior toxicologist in the monographs programme at the IARC and one of the authors of the study, says, "In the case of glyphosate, because the evidence in experimental animals was sufficient and the evidence in humans was limited, that would put the agent into group 2A."

But not everyone agrees?

An industry group of agrochemical companies called the Glyphosate Task Force said that the agency's evaluation "demonstrates serious deficiencies in terms of methodological approach and the overall conclusion is inconsistent with the results of all regulatory reviews concerning glyphosate's safety profile".

Monsanto — a member of the task force — said that relevant scientific data that showed no risk was excluded from the review, and the IARC "purposefully disregarded dozens of scientific studies", specifically genetic

toxicity studies.

But Guyton strongly defends the IARC process and insists that there is a set of clear rules that lays out which studies can be considered by the experts convened by the IARC. These are broadly limited to peer-reviewed publications and government reports, leading to the rejection of a number of industry-submitted studies.

Some academic scientists have sounded notes of caution over the IARC report. Oliver Jones, an analytical chemist at RMIT University in Melbourne, told the Science Media Centre in London: “IARC evaluations are usually very good, but to me the evidence cited here appears a bit thin.” He added: “From a personal perspective, I am a vegetarian so I eat a lot of vegetables and I’m not worried by this report.”

Doesn’t just about everything cause cancer if you look hard enough?

The IARC classifies compounds on a scale of decreasing certainty: group 1 is for agents that are definitely carcinogenic to humans; 2A, probably carcinogenic to humans; 2B, possibly carcinogenic to humans; 3, not classifiable; and 4, probably not carcinogenic to humans.

Monsanto said in its statement, “IARC has classified numerous everyday items in Category 2 including coffee, cell phones, aloe vera extract and pickled vegetables, as well as professions such as a barber and fry cook.”

But the IARC classified most of these items at the less dangerous 2B level, whereas glyphosate is in the 'probably carcinogenic' 2A category. Of Monsanto's list, only emissions from high-temperature frying and the occupational exposure experienced as a barber are rated as 2A.

What happens next?

It is not part of the IARC’s process to quantify any increased risk of cancer due to a chemical, or to recommend a safe exposure level, although its studies can be influential. Rather, regulatory agencies around the world will have to decide what to do with the agency’s finding. The US Environmental Protection Agency is currently conducting a formal review of the safety of glyphosate (which it does not consider carcinogenic in humans) and said that it would give “full consideration” to the IARC study.

Nature doi:10.1038/nature.2015.17181

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1. Guyton, K. Z. et al. *Lancet Oncol.* http://dx.doi.org/10.1016/S1470-2045(15)70134-8 (2015).
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Gustaf Deg • 2015-04-30 02:23 PM

I find the title to be quite misleading and sensational. "Linked to cancer" has a very different meaning than the classification "probably carcinogenic". This is not very helpful to a scientific discussion.

Peter Marchese • 2015-03-30 06:25 AM

I found the inclusion of cell phones ludicrous I thought this had long since been laid to rest. When we say something is a source of danger we should compare it to the benefits it brings, automobiles result in something like 25000 deaths a year in the USA but how many lives are saved by rapid road transport ?

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Nature ISSN 0028-0836 EISSN 1476-4687

Exhibit Q

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EcoWatch

EcoWatch

FOOD, GENETICALLY ENGINEERED FOODS, HEALTH

EPA Approves GMO Weed Killer Enlist Duo in Nine More States

Environmental Working Group | April 2, 2015 1:58 pm | Comments

Ignoring the World Health Organization's (WHO) conclusion that the crop chemical glyphosate is "probably carcinogenic to humans," the U.S. Environmental Protection Agency has approved the glyphosate-containing herbicide Enlist Duo for agricultural use in nine more states. It had previously been approved for use on genetically engineered crops in six states.

"Instead of taking steps to protect the public from toxic chemicals, the EPA has only sped up the pesticide treadmill that will now put millions more people at risk." Photo credit: Shutterstock

Enlist Duo's active ingredients are glyphosate and 2,4-D, both of which have been shown to increase the risk of non-Hodgkin lymphoma.

"This poorly conceived decision by EPA will likely put a significant number of farmers, farm workers and rural residents at greater risk of being diagnosed with cancer," said Scott Faber, senior vice president for government affairs at Environmental Working Group. "The agency simply ignored a game-changing new finding from the world leading cancer experts, and has instead decided the interests of biotech giants like Dow and Monsanto come first."

Last month, the International Agency for Research on Cancer, a branch of the WHO, elevated its risk assessment of glyphosate to "probably carcinogenic to humans" based on a review of the evidence by a panel of 17 leading oncology experts.

Glyphosate is the most used pesticide in the U.S. The bulk of it is applied to genetically engineered corn and soybean crops. It is also the main ingredient in Monsanto's signature weed killer RoundUp.

EPA's decision will allow Enlist Duo to be sprayed on fields of genetically engineered corn and soybeans in Arkansas, Kansas, Louisiana, Minnesota, Mississippi, Missouri, Nebraska, North Dakota and Oklahoma. It was previously approved for use in Illinois, Indiana, Iowa, Ohio, South Dakota and Wisconsin.

"Instead of taking steps to protect the public from toxic chemicals, the EPA has only sped up the pesticide treadmill that will now put millions more people at risk," added Faber. "These toxic herbicides easily make their way off farm fields and into the air and water we and our children breathe and drink."

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http://drleonardcoldwell.com/2...

Un-ethhical Practice? Absolutely!

One wouldn't expect a big corporate CEO to trade on Wall Street with inside information. Why, then, is America turning a blind eye to appointees holding office in the Food and Drug Administration and the Environmental Protection Agency whose resume pose serious compromises with their promise to uphold honest and ethical standards to ensure the safety of all Americans?

For the past two decades Monsanto has been plotting it's world domination and it's been easy so far, thanks to our government. Monsanto, a multinational agricultural biotech corporation, started as a small business in 1901 in St. Louis, Missouri, but it has transformed into a monopolizing mega monster. It's been an easy takeover because ever since the first Bush Administration, our presidents have been appointing ex-Monsanto lawyers, consultants, directors, chairmen, and CEOs to highly important positions in the FDA and EPA. So, what's the problem, you ask?

revolvingdoor

The problem is that these agencies that are supposed to have the American people's best interest and safety in mind, are essentially working for a big corporation, not us. They don't have our best interest in mind, they have Monsanto's in mind. They don't care about our safety, they care about Monsanto's financial reports. Are you disgusted yet? Perhaps you underestimate the extent of this abuse.

Former Monsanto Appointees to the FDA, USDA, and EPA

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heavyhanded • 8 months ago

EPA= Eliminating,Protection,for Americans.

2 • Reply • Share ›

BannedfromGLP ➔ heavyhanded • 8 months ago

Lol well what I'm learning now is how can we help the EPA be better. Unfortunately our systems aren't perfect, but if they really hated us they would take our opinions to heart. I am starting to believe these people only need help and facts. How can we contribute to them to find a better solution?

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nick quinlan ➔ BannedfromGLP • 8 months ago

The EPA is fully corrupt and does the bidding of the corporations it is supposed to regulate.

Welcome To The Revolving Door

Exhibit R

CENTER FOR FOOD SAFETY

May 2015 FACT SHEET

GLYPHOSATE AND CANCER RISK: FREQUENTLY ASKED QUESTIONS

WHY IS THERE CONCERN ABOUT GLYPHOSATE AND CANCER? The World Health Organization's (WHO's) cancer authorities – the International Agency for Research on Cancer (IARC) – recently determined that glyphosate is "probably carcinogenic to humans" (Group 2A). Glyphosate is the most heavily used pesticide in the world thanks to widespread planting of Monsanto's Roundup Ready crops, which are genetically engineered to survive spraying with it. Use and exposure will increase still more if glyphosate-resistant turfgrasses currently being developed for lawns, playing fields and golf courses are introduced.

WHERE DO EPA AND WHO'S IARC STAND ON GLYPHOSATE'S CARCINOGENICITY? In 1985, EPA classified glyphosate as a possible carcinogen based on experiments showing tumors in glyphosate-treated rodents. Input from Monsanto led to a dubious reinterpretation of these studies by EPA, and reclassification of glyphosate as non-carcinogenic in 1991.[1] IARC has thus far published only a brief summary of its glyphosate assessment, which is based on multiple lines of evidence: kidney, pancreatic and other tumors in glyphosate-treated test animals; epidemiology studies showing higher rates of cancer in glyphosate-using farmers; and research showing that glyphosate damages DNA and chromosomes, one mechanism by which cancer is induced.[2] IARC's full assessment is due out in 2016.

WHOSE ASSESSMENT IS MORE RELIABLE: IARC OR EPA? IARC is the world's leading authority on cancer. Its glyphosate determination was made by unanimous decision of 17 qualified scientists led by Dr. Aaron Blair, a distinguished epidemiologist recently retired from the U.S. National Cancer Institute.[3] IARC's assessment is up-to-date, analyzing all the relevant available research, while EPA's last comprehensive assessment of glyphosate occurred in 1993. IARC considered a broad range of evidence, including human epidemiology and other peer-reviewed studies, while EPA did not assess epidemiology and relied almost entirely on unpublished industry studies.[4] IARC is an independent agency whose sole mission is human health. While EPA is charged with protecting human health as well, it is also subject to considerable pressure from pesticide companies whose products it regulates. EPA is currently re-assessing glyphosate, and has said it will consider IARC's findings.

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HOW DOES GLYPHOSATE COMPARE TO OTHER AGENTS THAT CAUSE OR MAY CAUSE CANCER?

The evidence implicating glyphosate as a human carcinogen is not as strong as that for smoking or asbestos (IARC Group 1, "carcinogenic"), but stronger than that for DDT, parathion (both insecticides) or infection with type 2 HIV virus (Group 2B, "possibly carcinogenic").[5]

BUT DOESN'T IARC CONSIDER SUNLIGHT AND ALCOHOL TO BE CARCINOGENIC?

Although IARC primarily assesses chemicals, it also evaluates the carcinogenic potential of other "agents,"[6] which has unfortunately been used by some in a misguided attempt to cast doubt on its glyphosate determination. In fact, IARC's classifications of UV radiation and alcohol as "carcinogenic" are well-supported by science. Dermatologists regard excessive exposure to UV radiation (a component of sunlight) as the most important preventable cause of skin cancer.[7] According to the American Cancer Society, "alcohol is a known cause of cancers" of eight different organs.[8] The point is not that sunshine or drinking a few beers will kill you, but that you can reduce your risk of cancer by avoiding frequent sunburns and cutting back on heavy drinking. One important distinction here is that you can choose to wear sunscreen or drink less, but for most of us it is difficult to reduce our exposure to chemicals like glyphosate.

IS IARC'S ASSESSMENT RELEVANT TO ACTUAL HUMAN RISK OF CANCER?

A formal risk assessment evaluates both the inherent toxicity of a substance (called hazard) and our exposure to it. While a toxic substance is always hazardous, the risk it poses depends upon the circumstances of exposure.[9] While IARC does not directly evaluate exposure (it is a hazard assessment), it does consider the results of qualified epidemiological studies, which evaluate risk from actual exposure under real-world conditions. Three epidemiology studies of farmers show a link between glyphosate and non-Hodgkin's lymphoma (NHL), an immune system cancer.[10] Another finds a "suggestive association" between glyphosate and a related immune system cancer, multiple myeloma (but not NHL), and recommends follow-up given the herbicide's widespread use.[11] Because there is typically a time lag of decades between exposure to a carcinogen and elevated cancer rates, and glyphosate use has skyrocketed over the past 10-15 years, the full effects of glyphosate's rising use remain to be discovered.

IS THE GENERAL PUBLIC AT RISK FROM GLYPHOSATE?

Because of glyphosate's extremely intensive use (300 million lbs./year, more than four times that of the second-leading pesticide, atrazine), it is regularly found in food (e.g. bread), the air, rainfall and surface waters.[12] Glyphosate is found at similar frequencies and levels in the urine of farm and non-farm family members, including children, suggesting similar levels of exposure.[13] Glyphosate has also been detected in human blood.[14] EPA's maximal "safe" level of glyphosate exposure is six times higher than Europe's,[15] and 17.5-fold higher than the level EPA itself set in the early 1980s.[16] EPA's latest high-end estimate of infant exposure to glyphosate exceeds the level it regarded as safe in the 1980s;[17] and is five times higher than the maximum level suggested by independent scientists.[18]

ARE THERE OTHER PROBLEMS WITH GLYPHOSATE ASSESSMENTS?

EPA's assessments of glyphosate share the weaknesses of all the Agency's pesticide regulation. Most testing has involved only the active ingredient glyphosate, even though formulations (e.g. Roundup) used in the real world are often more toxic due to the presence of additional, often undisclosed, ingredients.[19] While we are all exposed to multiple pesticides in our food, water and air, EPA does not consider the additive or synergistic effects of exposure to glyphosate together with other pesticides. Finally, EPA's practice of basing its decisions almost entirely on studies conducted or commissioned by the pesticide registrant introduces serious conflicts of interest,[20] and excludes pertinent evidence from peer-reviewed studies by independent scientists.[21]

DO OTHER HERBICIDES POSE CANCER RISKS?

Massive use of glyphosate with Roundup Ready crops has generated an epidemic of glyphosate-resistant weeds. In response, pesticide companies are poised to introduce a host of "next-generation" GE crops resistant to herbicides such as 2,4-D and dicamba as well as glyphosate. These new GE crops will trigger an unprecedented and increasingly toxic spiral of weed resistance and herbicide use in American agriculture, for instance, a several-fold rise in 2,4-D and dicamba applications, with no countervailing reduction in glyphosate.[22] Exposure to 2,4-D and dicamba is linked to non-Hodgkin's lymphoma (NHL), the same cancer with which glyphosate has been associated.[23] Herbicide exposure in general is also linked to increased rates of Parkinson's disease.[24]

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[1] EPA (1991). Memorandum on Second Peer Review of Glyphosate, U.S. Environmental Protection Agency, 10/30/91.

[2] Guyton KZ et al. (2015). Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncology (March 20th), doi:10.1016/S1470-2045(15)70134-8.

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[4] EPA (1993). Glyphosate Reregistration Eligibility Decision. U.S. Environmental Protection Agency, Sept. 1993, App. C.

[5] See IARC List of classifications at http://monographs.iarc.fr/ENG/Classification/index.php.

[6] IARC also assesses biological organisms (e.g. viral infections), behavioral practices (e.g. tobacco smoking), occupational exposure (e.g. as firefighter), physical agents (e.g. surgical implants), and foods or components of food (e.g. coffee and caffeine), collectively referred to as "agents." See IARC Monongraphs on the Evaluation of Carcinogenic Risks to Humans, Preamble, at http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf.

[7] American Academy of Dermatology: Melanoma FAQs. https://www.aad.org/media-resources/stats-and-facts/conditions/melanoma-faqs.

[8] American Cancer Society: Alcohol Use and Cancer. The organs are the mouth, throat, larynx, esophagus, liver, colon, rectum and breast, see: http://www.cancer.org/cancer/cancercauses/dietandphysicalactivity/alcohol-use-and-cancer.

[9] Key factors include the timing and level of exposure. Children and fetuses are generally more susceptible to harm than adults; and while greater exposure is generally thought to mean greater risk, lower levels of hormone-disrupting chemicals sometimes cause more harm than higher levels (Vandenberg LN et al. 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocrine Reviews 33(3): 378-455).

[10] Guyton et al., 2015.

[11] De Roos AJ et al. (2005). Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environmental Health Perspectives 113(1): 49-54.

[12] For 2012 agricultural use of glyphosate (>280 million lbs.) and atrazine (70 million lbs.) in the U.S., see charts below maps at pertinent links on http://water.usgs.gov/nawqa/pnsp/usage/maps/compound_listing.php?year=2012&hilo=L. For non-farm uses of glyphosate (18-23 million lbs./year), see: EPA (2011). Pesticide Industry Sales and Usage: 2006 and 2007 Market Estimates, EPA, Feb. 2011, Tables 3.7 & 3.8. For glyphosate in food, see FoEE (2013). Human contamination by glyphosate. Friends of the Earth Europe, June 2013. For lack of testing in U.S., see: Gillam C (2015). Regulators may recommend testing food for glyphosate residues, Reuters, 4/20/15. For glyphosate in air, rain and surface water, see Chang F-C et al. (2011). Occurrence and fate of the herbicide glyphosate and its degradate aminomethylphosphonic acid in the atmosphere. Environ Toxicol Chem 30(3): 548-555; and Coupe RH et al. (2011). Fate and transport of glyphosate and aminomethylphosphonic acid in surface waters of agricultural basins. Pest Manag Sci 68(1): 16-30.

[13] Curwin BD et al. (2007a). Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in Iowa. Ann. Occup. Hyg. 51(1): 53-65; and Curwin BD et al. (2007b). Pesticide dose estimates for children of Iowa farmers and non-farmers. Environmental Research 105: 307-315. For Europe, see FoEE (2013). Human contamination by glyphosate. Friends of the Earth Europe, June 2013.

[14] Aris A, Leblanc S. Maternal and fetal exposure to pesticides associated to genetically modified foods in Eastern Townships of Quebec, Canada. Reprod Toxicol. 2011: 31(4): 528-533.

[15] "Acceptable daily intake" (ADI) or the equivalent "chronic population adjusted dose" (cPAD), expressed as milligrams glyphosate per kilogram body weight per day: 0.3 in Europe vs. 1.75 mg/kg/day in the U.S. For Europe, see http://ec.europa.eu/food/plant/protection/evaluation/existactive/list1_glyphosate_en.pdf, Appendix II; for US, see EPA (2006). Glyphosate human health risk assessment for proposed use on Indian mulberry and amend use on pea. EPA, 9/29/06, p. 21.

[16] For EPA's setting of the glyphosate ADI at 0.1 mg/kg/day in the early 1980s (vs. 1.75 today), see EPA (1983). Glyphosate (Roundup) on wheat. March 3, 1983.

[17] See EPA (2006) in footnote 14, Table 6.1.2, maximum infant exposure = 0.127562 mg/kg/day, 28% higher than the 1980's ADI of 0.1 mg/kg/day (see EPA 1983 in last footnote).

[18] Antoniou M et al. (2012). Teratogenic effects of glyphosate-based herbicides: divergence of regulatory decisions from scientific evidence. J Environ Anal Toxicol S4:006. doi:10.4172/2161-0525.S4-006, suggesting an ADI of 0.025 mg/kg/day based on teratogenic rather than carcinogenic effects.

[19] See references at: http://earthopensource.org/gmomythsandtruths/sample-page/4-health-hazards-roundup-glyphosate/4-2-myth-strict-regulations-ensure-exposed-safe-levels-roundup/

[20] Boone MD et al. (2014). Pesticide regulation amid the influence of industry. BioScience 64: 917-922.

[21] Myers JP et al. (2009). Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A. Environmental Health Perspectives 117(3): 309-315.

[22] Mortensen DA et al. (2012). Navigating a critical juncture for sustainable weed management. Bioscience 62(1): 75-85.

[23] Schinasi L, Leon ME (2014). Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis. Int. J Environ. Res. Public Health 11: 4449-4527. McDuffie HH et al (2001). Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiology, Biomarkers & Prevention 10: 1155-1163.

[24] For instance, see: Brighina L et al. (2008). Alpha-synuclein, pesticides and Parkison disease. Neurology 70: 1461-1469.

Exhibit S

Stocks | Wed Jun 24, 2015 9:19am EDT

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CORRECTED-WHO unit finds 2,4-D herbicide 'possibly' causes cancer in humans

(Corrects 9th paragraph to drop words "epidemiological studies" to reflect that evidence was not derived from those types of studies)

By Carey Gillam

A widely used farm chemical used as a key ingredient in a new herbicide developed by Dow AgroSciences "possibly" causes cancer in humans, a World Health Organization research unit has determined.

The classification of the weed killer, 2,4-dichlorophenoxyacetic acid, known as 2,4-D, was made by the WHO's International Agency for Research on Cancer (IARC).

The IARC said it reviewed the latest scientific literature and decided to classify 2,4-D as "possibly carcinogenic to humans," a step below the more definitive "probably carcinogenic" category but two steps above the "probably not carcinogenic" category.

IARC's findings on 2,4-D have been awaited by environmental and consumer groups that are lobbying U.S. regulators to tightly restrict the use of 2,4-D, as well as by farm groups and others that defend 2,4-D as an important agent in food production that does not need more restrictions.

In March, IARC said it had found another popular herbicide -glyphosate - was "probably carcinogenic to humans." Glyphosate is the key ingredient in Monsanto Co's Roundup herbicide and other products.

IARC classifications do not carry regulatory requirements but can influence regulators, lawmakers and the public. Following the glyphosate classification, some companies and government officials moved to limit glyphosate use.

Dow AgroSciences, a unit of Dow Chemical Co, has had a particular interest in IARC's review. The company is using both glyphosate and 2,4-D in a herbicide it calls Enlist Duo that received U.S. approval last year. Enlist Duo is designed to be used with genetically engineered, herbicide-tolerant crops developed by Dow.

Dow had no comment on the IARC classification, but the company has said 2,4-D is a safe and valuable tool for agriculture.

IARC said it decided on the "possibly" classification because there was "inadequate

evidence in humans and limited evidence in experimental animals" of ties between 2,4-D and cancer. It said that there is "strong evidence that 2,4-D induces oxidative stress ... and moderate evidence that 2,4-D causes immunosuppression ..."

However, IARC said, "epidemiological studies did not find strong or consistent increases in risk of NHL (non-Hodgkin lymphoma) or other cancers in relation to 2,4-D exposure."

Dana Loomis, a deputy section head for IARC, said the most important studies reviewed showed mixed results, and a "sizable minority" judged the evidence as stronger than others did.

Among the research presented to IARC was an analysis funded by a Dow-backed task force that found no ties between 2,4-D and many cancers.

Some critics of 2,4-D had thought IARC would assign at least the "probably" cancer-causing classification to 2,4-D. But the Dow-backed task force said there was no reason to do so.

"Not one health and safety regulator in the world consider 2,4-D to be a human carcinogen," the 2,4-D Research Task Force said in a statement.

Since its introduction in 1945, 2,4-D has been widely used to control weeds in agriculture, forestry, and urban and residential settings. (Reporting by Carey Gillam; Editing by Steve Orlofsky)

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Exhibit T

PRODUCERS

Busted: EPA Discovers Dow Weedkiller Claim, Wants It Off The Market

November 25, 2015 · 4:09 PM ET

DAN CHARLES

Soybeans are sprayed in Iowa in 2013. Enlist Duo is a mixture of two chemicals that farmers have used separately for many years: glyphosate (also known as Roundup) and 2,4-D. The new formulation is intended to work hand-in-hand with a new generation of corn and soybean seeds that are genetically engineered to tolerate sprays of both herbicides.

Charlie Neibergall/AP

Ever been caught telling different stories to different people? It's awkward.

Dow AgroSciences, which sells seeds and pesticides to farmers, made contradictory claims to different parts of the U.S. government about its latest herbicide. The Environmental Protection Agency just found out, and now wants to cancel Dow's legal right to sell the product.

The herbicide, which the company calls Enlist Duo, is a mixture of two chemicals that farmers have used separately for many years: glyphosate (also known as Roundup) and 2,4-D. It's Dow's answer to the growing problem of weeds that are resistant to glyphosate, which has become the weed-killing weapon of choice for farmers across the country.

The new formulation is intended to work hand-in-hand with a new generation of corn and soybean seeds that are genetically engineered to tolerate sprays of both herbicides.

THE SALT

European Cancer Experts Don't Agree On How Risky Roundup Is

THE SALT

Farmers Face Tough Choice On Ways To Fight New Strains Of Weeds

When Dow applied for permission to sell Enlist Duo in 2011, it told the EPA that this mixture of glyphosate and 2,4-D is no more toxic than the two chemicals are, if considered separately. The EPA accepted that argument and approved the new herbicide just over a year ago. Dow began selling it, in small quantities, this year.

But the decision was controversial. Environmentalists argued that Enlist Duo would bring on a massive increase in herbicide use. Some farmers were concerned about the use of 2,4-D, because that chemical is known to blow into neighboring fields.

Several environmental groups went to court to overturn the EPA decision, arguing that combining these two chemicals could result in new "synergistic" toxic effects that the EPA had ignored. And in the course of that litigation, the EPA discovered that Dow had been telling the U.S. Patent and Trademark Office a different story.

When applying for a patent, an inventor needs to show that something is novel and useful. And Dow's patent application for Enlist Duo claims that this mixture of chemicals does, in fact, offer farmers something new: "synergistic herbicidal weed control."

Last month, the EPA asked Dow to explain these synergistic effects. On Nov. 9, the company responded with what the EPA calls "extensive information." Neither Dow nor the EPA has disclosed any details, but the EPA, after taking a look at the new

information, decided to ask the court for a chance to reverse its approval of Enlist Duo until it had fully evaluated the new information. The agency suggested that it may require larger safety buffers around fields where Enlist Duo is used.

The EPA's decision stunned both foes and friends of the new herbicide.

The herbicide's opponents, among them the Pesticide Action Network, the Center for Food Safety and the Center for Biological Diversity, celebrated.

Dow, in a brief email statement, said that it is working with EPA to provide assurance that the product is safe and that "we expect that these new evaluations will result in a prompt resolution of all outstanding issues."

herbicide soybeans environmental protection agency dow

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